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November 12, 2020

Christopher A. Lott
Deputy General Counsel
Duke University
310 Blackwell Street, 4th Floor, Box 104124
Durham, North Carolina 27710

VIA email: chris.lott@duke.edu

Re: Wei Jiang, M.D.

Dear Mr. Lott:

Along with Robert Levin, with Haywood, Denny & Miller, LLP, I represent Dr. Wei Jiang, a tenured professor and clinical psychiatrist employed by the Duke University Medical School for more than thirty years, since 1989. The purpose of this letter is to bring to your attention recent events regarding Dr. Jiang's terms and conditions of employment and her belief that she has been subjected to a hostile and discriminatory work environment by her employer, primarily through the actions of Dr. Moira Rynn, the chair of the Department of Psychiatry, which have been ratified by the Dean of the Medical School, Mary E. Klotman.

Dr. Jiang joined Duke on September 01, 1989 as Research Associate. She began a Formal Residency training on July 01, 1997 with the Duke Medicine & Psychiatry Combined Training Program. On July 1, 2002, Dr. Jiang was hired at a salary of $105,000.00. On February 01, 2012, Dr. Jiang was promoted to Associate Professor with Tenure (Track II). Two years later, on July 1, 2014, Dr. Jiang was promoted to Full Professor with Tenure (Track II).

Dr. Jiang's salary increased virtually every year until after Dr. Rynn was hired as Department chair.

DATE	**SALARY**	**NOTE**
July 01, 2003	$125,000.04	
July 01, 2004	$128,450.04	
July 01, 2005	$132,000.00	
July 01, 2006	$140,000.00	**Promoted Associate Professor on Tenure Track II**

DATE	SALARY	NOTE
July 01, 2007	$144,900.00	
July 01, 2008	$150,405.96	
October 01, 2009	165,456.00	
March 01, 2010	$173,728.80	
July 01, 2011	$178,940.64	
July 01, 2012	$178,940.64	
July 01, 2013	$182,519.40	
July 01, 2014	$186,169.80	
July 01, 2015	$190,824.00	
July 01, 2016	$195,594.60	
Sometime in late 2016		**Moira Rynn selected as Chair of Psychiatry**
July 01, 2017	W. Jiang salary $200,484.48	
July 01, 2017		**Moira Rynn hired at Duke as Psychiatry department Chair**
September 01, 2017	$136,523.40	**salary decreased from $200,484.48 to $136,523.40; a 31.9% reduction.**
December 01, 2017	$148,907.28	
April 18, 2018		**M. Rynn requests audit of W. Jiang's REMIT research**
July 01, 2018	$152,629.92	

DATE	SALARY	NOTE
July 01, 2019	$34,418.00	**Salary decreased from $152,629.92 to $34,418.00, a 77.5% reduction after Moira Rynn unilaterally terminated a grant received by Dr. Jiang which had an initial year value of almost $800,000.**
July 01, 2020	$34,418.00	

Since 2004, Dr. Jiang has taken annual to bi-annual trips to China to collaborate with colleagues, provide mental health outreach, and attend conferences, usually presenting at the same. She has combined these trips with a trip to visit her family. In 2018, Dr. Jiang left for her usual trip to China on April 2, 2018.

Dr. Jiang was travelling in China when she saw Dr. Rynn's announcement that Dr. Scott Kollins would be stepping down as Vice Chair for Research for the Department of Psychiatry. Dr. Jiang immediately emailed Dr. Rynn and expressed interest in the position being vacated by Dr. Kollins. Dr. Rynn replied to her Dr. Jiang's email in non-committal manner. [1] (It should be noted that Dr. Rynn has not replaced Dr. Kollins and this has enabled her to engage with impunity in the behavior described in this letter. Dr. Rynn's photo, along with the photos of Scott Compton, Ph.D., Clinical Research Unit (CRU) Director and Alifia Hasan, MBA, the Research Practice Manager, appear on a page denominated "Research Leadership" indicating that more than two years later, Dr. Rynn is still serving as the interim Vice Chair for Research for the department.)

Apparently, soon after Dr. Jiang's inquiry about the Vice Chair for Research position, Dr. Rynn then initiated a human subject compliance review/audit of protocol for QA Review for Dr. Jiang's research study Pro00009555 Responses of Myocardial Ischemia to Escitalopram Treatment (the primary REMIT study) located in Department of Psychiatry and Behavioral Sciences Clinical Research Unit (CRU) and

[1] (It should be noted that Dr. Rynn has not replaced Dr. Kollins and this has enabled her to engage with impunity in the behavior described in this letter. Dr. Rynn's photo, along with the photos of Scott Compton, Ph.D., Clinical Research Unit (CRU) Director and Alifia Hasan, MBA, the Research Practice Manager, appear on a page https://psychiatry.duke.edu/research/research-leadership denominated "Research Leadership" indicating that more than two years later, Dr. Rynn is still serving as the interim Vice Chair for Research for the department.)

funded by the National Heart, Lung, and Blood Institute (NHLBI). (Dr. Rynn in fact informed Dr. Jiang that she has been the source of the initiation of the review, even though she knew there has been no misconduct, during a conversation on January 29, 2020.) In addition, Dr. Jiang was also working on a related study called the REMIT repository trial which was funded to collect the data for the primary trial Pro00009555 for use in future research studies.[2]

Dr. Jiang was notified about the departmental audit on April 18, 2020, when she was copied on an email from Sharikia Burt, Assistant Research Practice Manager for the Department of Psychiatry and Behavioral Sciences to Pamela Bonner, the research coordinator for Dr. Jiang's lab from May 2017 to May 1, 2018. The email indicated that Burt knew Dr. Jiang was still in China but that Burt was scheduling a time to "do an internal review of the study file for the REMIT study." Sharikia Burt reported directly to Dr. Rynn who was serving as the interim vice chair in due to the departure of Scott Kollins.

Dr. Jiang returned to her office on April 25, 2018, and was told by Dr. Jeannie Beckham, the division chief of for Dr. Jiang's division of Behavioral Medicine, that Pamela Bonner had made a complaint to Dr. Rynn that Dr. Jiang did not "know how to manage a laboratory." (In fact, Bonner later denied to Dr. Jiang that she had made any complaints about the lab practices under Dr. Jiang.) Beckham stated that as a result of Bonner's complaint, Pamela Bonner was going to move to another lab. She implied that Bonner's complaint was the reason for the internal audit. Dr. Jiang expressed shock to Dr. Beckham that Bonner had made negative statements about her and indicated she wanted to speak to Bonner about her concerns about the lab. Beckham told Dr. Jiang that she should not do so because Dr. Jiang could be seen as retaliating against Bonner. As a result, Dr. Jiang made no inquiries to Bonner about her knowledge about issues in the lab or the audit itself. Bonner in fact transferred to another lab on May 1, 2018, as had been planned prior to Dr. Jiang's trip to China.[3]

Upon Dr. Jiang's return, Dr. Rynn requested to meet with her on April 30, purportedly to discuss the internal department audit findings on REMIT study by Sharikia Burt. This report, however, was not actually submitted by Burt until May 3, 2018, several days after the meeting. At the meeting on April 30, Dr. Rynn then

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[2] Access to the data collected under both studies was taken from Dr. Jiang at Dr. Rynn's instigation after the Office of Audit, Risk & Compliance report was delivered in September 2018. All data has been sequestered since then and Dr. Jiang has had no access to it.

[3] It should likewise be noted that Jean Beckham, Ph.D., is listed as a co-division director of Dr. Jiang's division (Behavioral Medicine & Neurosciences) along with Dr. Rynn, who again is listed as the interim co-division director. Serving in this interim capacity and supervising Beckham again has facilitated Dr. Rynn's termination of Dr. Jiang's research career.

informed Dr. Jiang that Dr. Rynn wanted to refer the department audit report to the Duke Office of Audit, Risk & Compliance (OARC) to undertake an additional audit of the REMIT study and suggested that the OARC audit would be a way for Dr. Jiang to improve her research. Dr. Jiang decided not to oppose Dr. Rynn in this matter. Dr. Jiang did NOT agree to the audit nor request it. At the time, she had no idea about Dr. Rynn's intentions towards her, nor that she had instigated the original audit, and not Pamela Bonner, Dr. Jiang's research coordinator.

Nevertheless, the very next day, on May 1, prior to the finalizing of the report by Burt and prior to Dr. Jiang actually seeing the report, Dr. Rynn sent an email to David Falcone, Director of Ethics and Compliance and the University Compliance Officer, and Leigh Goller, the Chief Audit, Risk and Compliance (OARC) Officer, which stated "Dr. Jan Jiang and I are requesting that your assistance and request that your team conducts an audit for Protocols #00014033 and #00009555." Falcone replied asking either Dr. Jiang or Dr. Rynn to call him with more details.

Dr. Rynn emailed Dr. Jiang and told her that there was no need for her to contact Falcone which Dr. Jiang understood that Dr. Rynn was purposefully preventing her from having contact with anyone in the University audit office. Again, it should be noted that Dr. Rynn purposefully misled Falcone and Goller when she stated that Dr. Jiang had joined Dr. Rynn in requesting the audit.[4] At that time, Dr. Jiang was unaware of the actual conclusions of the departmental audit and unaware that most of the issues involved the organization of the study file and were easily correctable.

Burt's memo to Dr. Jiang and Steve Boyle noted that 10 subjects were enrolled in the study at the time of her review. In fact, there were 310 subjects enrolled as Burt's memo later states. In fact, Burt only reviewed the files of 10 subjects and did not, as she indicated, review any electronic files. Burt's findings concerned 1) the contents of the regulatory binder, 2) the subject data and documentation, and three 3) miscellaneous comments regarding issues such as the ink color used and proper strike-through method of correcting errors. No comments were made about any failure by Dr. Jiang to provide oversight as the PI or that ineligible subjects were enrolled in the study.

Below is a chart listing the issues noted in the initial report of the Department of Psychiatry and Behavioral Sciences Clinical Research Unit authored by Burt, who reported to Dr. Rynn.

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[4] I would note that Dr. Rynn's actions are NOT protected under the Duke Non-retaliation and Non-retribution Policy which provides that if "someone purposely contrived, exaggerated, or otherwise disseminated a report of wrongdoing – whether to protect themselves or to hurt someone else – that person will NOT be protected under the policy."

REPORT FINDING	RESPONSE
CONTENTS OF REGULATORY BINDER	
Delegation of Authority (DOA) Log not created at time of IRB approval.	There is no evidence to support the conclusion that no delegation of authority log was created. Burt assumed this because she could not find it, while acknowledging that Bonner "re-created" the log in December 2017. There is also no support for the recommendation that an Note to File needed to be created stating that the log was not created or that there was a protocol deviation reportable to the IRB.
Omission of CVs, licenses, trainings from regulatory binder	This comment acknowledged that a DOA log did in fact exist, contrary to the above finding. In addition, the report acknowledged that at the time of the study, the electronic IRB system did not exist and that all IRB approvals and submissions were in the regulatory binder post-eIRB implementation.
RDSP plan not in regulatory binder.	This comment implicitly acknowledged that the plan existed but was simply not in the binder.
DSMB reports not in regulatory binder.	This comment implicitly acknowledged that the reports existed but were simply not in the binder.
Package inserts for study drug not in regulatory binder.	No recommendation was made, but presumably insertion of the insert into the binder was easily correctable.

REPORT FINDING	RESPONSE
ClinicalTrials.gov documentation not in regulatory binder.	The recommendation was to add the documentation to the binder and easily correctable.
There was no finding that all relevant IRB correspondence was not in the binder.	The recommendation was to ensure that all IRB correspondence was in the binder and easily correctable. Previous findings had indicated that all IRB approvals and submissions post eIRB implementation were up to date and complete.
SUBJECT DATA AND DOCUMENTATION	
The report inconsistently stated that none of the ten reviewed subjects had documentation of the informed consent process and also that the subject informed consents were in fact filed in the appropriate subject folders.	No recommendations or action items were noted, other than "for future reference" include two subject identifies on the consent forms for each patient.
Subject data was not checked on the shared drive, but the conclusion was reached that documentation was incomplete.	The recommendation was to confirm the process for accessing and combining the paper documentation and the electronic documentation in case of audit and to organize the study file, therefore acknowledging the role that the transition from paper to electronic data storage affected the file's organization.
The propriety of enrolling a subject unable to come off beta blockers and unable to complete the exercise stress test was raised as an issue for exclusion from the study.	The IRB amendment policy in effect now and since 2016 clearly indicates that changes to the protocol "necessary to eliminate apparent immediate hazards to the subject (45 CFR 46.103(b)(4)(iii) and 21 CFR 56.108(a)(3)-(4))" do not require IRB review and approval which

REPORT FINDING	RESPONSE
An issue regarding mailing study medication was also raised.	is what the beta blocker and exercise stress testing requirement changes were: changes necessary to insure patient safety. The recommendation was to confirm that mailing was allowed and whether mailing SOPs existed.
Enrollment logs provided via email were not complete.	Recommendation was to ensure all data was entered on logs.
Adverse Events (AE) were documented; Serious AE documentation was not present at review.	The assumption was made that the SAE's were not properly documented; this was without factual basis and assumed because the audit could not review the documentation. The recommendation should have been to locate the documentation, not to report missing documentation as a protocol deviation to the IRB if the documentation actually existed.
No protocol deviations were documented.	Protocol deviations necessary to protect patient safety did not require advance IRB approval per even the 2016 policy. The recommendation was to create a log to track protocol deviations, which was easily accomplished.
MISCELLANEOUS	
Pencil or purple ink was used.	Recommendation was to use black or blue ink.
Errors were not corrected appropriately.	Errors should be corrected by striking through them with a single line and initialing and dating them.

REPORT FINDING	RESPONSE
No comment was included about notes to the file.	A recommendation was made that memos to the file (notes to the file) had standard contents.

Burt's May 3rd report recommended escalation of the audit to the Office of Audit, Risk & Compliance (OARC) for review of "data integrity, subject safety and concern for proper PI oversight." As noted above, Burt's report contained no comments about PI oversight; this comment appears to have been the suggestion of Dr. Rynn who supervised Burt. And again, in an email to David Falcone, on May 1, Dr. Rynn indicated that **she and Dr. Jiang** were requesting the escalation. Again, Dr. Jiang did not even receive a copy of the departmental audit report by Burt until the afternoon of May 4, after Dr. Rynn had already escalated the matter to the OARC.

The engagement team for the audit was composed of David Falcone, the University Compliance officer, Leigh Goller, the Chief Audit, Risk & Compliance Officer, and two auditors, Nancy Shelton and Sally Scherer-Pinsley. On June 12, 2018, the auditors assessed compliance, visiting the Department of Pharmacy Investigational Drug Services (IDS) and reviewed regulatory documents for the REMIT study. Between July 3 and July 7, 2018, the OARC RCA auditors continued their audit. by visiting the Psychiatry research offices and reviewed additional regulatory documents for the REMIT study.[5]

Meanwhile, in early July, while the OARC audit was ongoing, the National Heart, Lung, and Blood Institute (NHLBI) asked Dr. Jiang to submit the JIT[6] for Dr. Jiang's new R01 application. A JIT is processed by the department Clinical Research Unit (CRU), which Dr. Jiang understood was undergoing personnel changes at that time. As a result, the JIT submission process proceeded quietly slowly unfortunately. Dr. Jiang was unaware that Dr. Rynn was still serving as the interim Vice Chair for Research after Scott Kollins had stepped down as Vice Chair for Research.

On August 9, the program officer for the NHLBI sent Dr. Jiang a message inquiring about the timing of the Duke IRB response to the JIT request. Dr. Jiang reached out

[5] The rule report was not issued until September 2018.

[6] JIT refers to "just in time," refers to the application timeframe requiring applicants to send updated information to a grant source if an award is likely, thereby providing the grant source with the most current information "just-in-time" for award.

to Terry Ainsworth, the IRB director, about the response and was told on August 10, 2018:

> The (Duke) IRB generally takes 30 days, but we hope for your protocol to be initially approved by the end of the day. If it isn't, it should be completed by Monday. Terry.

Dr. Jiang then sent the NHLBI program officer that information, explaining:

> We have to take a notably longer time for it related to my study manager went on vacation last Wednesday, the departmental CRU lead staff is leaving the position, and the Duke eIRB is switching to a new electronic system.

Dr. Jiang forwarded copies of these e-mail messages to Dr. Rynn, per Dr. Rynn's request, to let her know that the program officer had responded that the NHLBI expected "to be able to fund your study, pending IRB approval (although this is not a guarantee of course). Congratulations and have a good weekend." and asked Dr. Rynn, of course, to keep the communication confidential.

Apparently, Dr. Jiang's message to the NHLBI program officer offended Dr. Rynn who apparently took it as a criticism of her in her position as Vice Chair over the CRU. After Dr. Rynn saw the message, she emailed Dr. Jiang to request an urgent meeting with the presence of Dr. Jeannie Beckham, now the co-chair along with Dr. Rynn as interim, of the Behavioral Medicine and Neurosciences division of the Department of Psychiatry, but at that time, Division Chief for the division. The purpose of the meeting was "to discuss with Jeannie preparing for your new grant and the other issues you have raised with me."

At the meeting on Monday, August 20, 2018, Dr. Rynn explained to Dr. Jiang that she was filling the CRU director position on an interim basis. She told Dr. Jiang that she was the Chair of the Department and that she had power to terminate Dr. Jiang's grant. Dr. Rynn then accused Dr. Jiang of telling the NHLBI program officer that the Department of Psychiatry CRU director (i.e., Dr. Rynn) was not capable. Dr. Jiang of course denied the same and after the meeting, Dr. Jiang then emailed Dr. Rynn and attempted to clarify her email to the NHLBI program officer:

> I thought it is necessary for me to bring it to your attention that I did not say anything about we do not have a CRU director to my PO. I said the "CRU lead staff". Please see the specific piece here (bold are). I hope it clarifies. Your comment has made me very uneasy. Jan

Dr. Rynn never responded to Dr. Jiang's email or her concern about Dr. Rynn's threat to terminate Dr. Jiang's new grant.

On September 10, 2018, Dr. Jiang became aware that the OARC audit report had been completed when she received a copy of the Executive Summary. Dr. Rynn requested to meet with Dr. Jiang, along with Beckham and Steve Boyle (Jiang's team statistician and laboratory manager), Terry Ainsworth (Duke IRB management Director), and Dr. Jen Ellis (Psychiatry department vice chair for finance, who attended via telephone) to review the audit report and discuss Dr. Jiang's response to the report.

Dr. Jiang was not provided the complete report until September 12, 2018. Notably, the report concluded that "[o]verall, we observed ***no significant patient safety concerns***." The report also noted "conflicting information and gaps in documentation indicate issues related to protocol adherence." Finally, the report noted that the REMIT study was "a relatively low patient safety risk trial evaluating an approved and widely used antidepressant . . . ." The Executive Summary raised issues regarding "subject eligibility; the consenting process; data integrity; distributing, destroying and tracking drug; protocol lapse; and serious noncompliance never reported to the IRB. Of reviewed cases, OARC identified eligibility issues in 84%, procedures not performed per protocol in 92%, and documentation inconsistencies in 100%."

Notably, the audit covered two separate studies: one specifically and primarily studying the efficacy of escitalopram on mental stress-induced myocardial ischemia (MSIMI) in patients with stable ischemic coronary heart disease (SICHD) and another which created a repository for data collected during the primary trial but not used in the primary trial. The audit report reviewed 25 of the patients participating in the study out of 307 for the repository study and 127 for the primary trial. A summary of the findings and issues with the findings appears below.

REPORT FINDING	**RESPONSE**
PATIENT ELIGIBILITY OBSERVATION	
A safety checklist found in the study documents was not incorporated into the protocol.	The report admitted that it was not clear that the checklist document was actually used or was a part of the protocol

Patients were determined to be "ineligible" if they did not complete the exercise stress tests or stop beta blockers before mental or exercise stress testing.	In fact, the investigators amended the protocol to omit the eligibility requirement that the participants stop beta blockers or be required to undergo exercise stress testing in consideration of safety of patients consistently. If the patient at baseline used beta blockers, then endpoint evaluation was also done with the use of beta blockers. Because the primary purpose of the study was the evaluation of mental stress, exercise stress testing was not required to evaluate the hypothesis. The beta blocker and exercise testing components were not necessary for the primary study and were taken into account in the data collection for secondary purposes of investigation. Finally, even the current IRB policy from 2016 does not even require prior IRB approval of amendments which are necessary to protect patient safety. See IRB policy "Amendments to Previously Approved Research," current as of 03.01.2016. In addition, see IRB policy "Problems or Events That Require Prompt Reporting to the IRB, " (current as of 08.09.2019, (hereinafter IRB policies). See also 45 C.F.R. § 46.108(a)(4)(i) (reporting required for unanticipated problems involving risks to subjects) and 46.108(a)(3)(iii)(prompt reporting to IRB not required when necessary to eliminate hazards to subject); 21 C.F.R. § 56l.108(b)(1) (requiring IRB notification of unanticipated problems involving risks to subject in FDA

	regulated clinical investigations) (hereinafter CFR regulations).
The documentation of the MSIMI was "missing."	In fact, all of the information was available but in different locations due to the transition from paper to electronic format during the study, due to the turnover in staff and different practices for maintaining the data, and due to the required study move in locations in the middle of the study.
Missing documentation of Medication Washout/Withdrawal	The exclusion criteria referred to as supporting this conclusion was amended during the study and subjects were not required to withhold medications for safety reasons. See CFR regulations and IRB policies above.
Missing documentation of physician approval	This documentation did in fact exist, but was not obvious to the audit team.
The overall conclusion that 84% of the 25 reviewed had eligibility issues.	This conclusion was simply false. All patients were eligible for the purposes for which their data was collected which was different depending on whether they participated in the repository study or the drug vs placebo study involving MSIMI. The ineligibility conclusion was based on the application of the original protocol which was changed due to patient safety concerns.
DATA QUALITY OBSERVATION	

The report stated that it was difficult to fully assess protocol compliance and data integrity.	The study begin in 2006 prior to any of the institutional requirements that the 2018 audit team applied to the study. As just one example of this, a review of the Duke Office of Clinical Research policies shows that none of the policies were in effect between 2006 and 2011 while the studies were enrolled and ongoing. Moreover, the audit admitted that it was "common to amend forms throughout the life cycle of a trial." The audit team also failed to take into consideration the transition during the trial from paper to electronic record keeping. Moreover, the amendments to the protocol were a result of patient safety concerns.
PROCEDURES AND STUDY VISITS NOT DONE / NOT PERFORMED PER PROTOCOL	
The audit concluded that the procedures and study visits specified in the protocol was not performed in 91% or 23 of the patients reviewed.;	In addition, the audit repeated a finding from an earlier report that had in fact been made to the IRB. Again, the audit team ignored the fact that the protocol was in fact amended by the investigators See IRB policies and CFR regulations above. In addition, see https://irb.duhs.duke.edu/irb-review-process/faqs/reporting-irb which states that protocol deviations or violations must be reported if they: (i) affects subject rights and welfare, or (ii) affects subject safety; or

	(iii) affects the integrity of study data; or (iv) affects the subject's willingness to continue in the study; or (v) s specifically requested by a government agency, internal/external auditor, medical monitor, or the IRB. None of the protocol deviations met any of the above criteria.
CONSENT FORMS AND PROCESS	
Of the 134 informed consents reviewed, only 17 had an issue as identified by the audit team.	The recommendations made included changes to policy which were not in place at the time of the REMIT study.
IRB LAPSE IN APPROVAL AND ENROLLMENT	
The audit team included an item about a matter previously reported to the IRB and addressed.	The audit team was unable to find the documentation and then without basis concluded that it did not exist. Moreover, the matter had already been reported to the IRB.
SAFETY REVIEW FOR FIRST 20 PATIENTS	
A safety review was not conducted.	Again, because the audit team could not easily locate source documentation, and erroneously it concluded that the review did not occur.
DRUG ACCOUNTABILITY ISSUES	
Drugs were mailed in violation of the protocol.	The protocol was changed to allow dispensing by mail. See CFR regulations and IRB policies above.

DSMB DOCUMENTATION OF REVIEW/APPROVAL	
The REMIT trial was responsible for missing DSMB documentation.	In fact, the audit admitted that the DSMB chair provided letters indicating approval for each year which were one file.
REGULATORY BINDERS	
Paper and electronic binders were poorly organized.	The report admitted that transition from paper to electronic storage of data was a factor in the organization of the study data.
DATA SECURITY PLAN UNTIMELY INCOMPLETE	
RDSP requirement was not followed.	The report admitted that the RDSP requirement was not implemented until 2011 after the REMIT study enrollment was concluded.
SS # POLICY	
The report did not indicate how the policy was violated.	The files reviewed were kept secure and not open to review by anyone not approved to view them. The storage approval authorization process policy was not adopted until April 2015.
ONE DUKE EMPLOYEE ENROLLED	
Duke employee was enrolled.	In fact, the report admitted that the IRB could have approved enrollment of the employee under the previous and former versions of the policy.

ADVERSE EVENTS REPORTED INCORRECTLY	
The audit concluded that two "adverse events" occurred and were documented but were reported incorrectly.	The report was not certain that one of the patients actually had an adverse event; the other patient had nausea and it was included in the notes, but not on an adverse event form. The current policy, last updated in August 2019, only requires the reporting of adverse events that are "serious, unexpected and related to a drug administration as part of a clinical trial." In addition, see https://irb.duhs.duke.edu/irb-review-process/faqs/reporting-irb "An Adverse Event must be reported to the IRB if it: (i) is more likely than not related to study activities; and (ii) represents a new risk; and (iii) is unanticipated. In addition, an expected event that is occurring at a frequency or intensity greater than originally anticipated must be reported to the IRB." Arguably neither of the noted "events" met the above definition; nonetheless they were clearly documented.
DR. JAMES JOLLIS DID NOT PERFORM ECHOCARDIOGRAMS	
Protocol specified Dr. James Jollis.	The protocol was changed to allow other cardiologists to perform because Dr. Jollis was unable to do so.
LOST SAMPLES	

Three tubes of blood were lost.	Because the documentation that the samples were lost was not found by the audit, the report concluded that the lost tubes were not reported to the IRB.

Clearly, the only issues of any import in the report related to the report's erroneous conclusion that the protocol was not followed. In fact, the original protocol used changed over the study's lifetime in ways that only positively affected patient safety. The only residual issues from the report involved the erroneous conclusion that "ineligible" patients had been enrolled. This was clearly not the case. The discontinuation of beta blockers and the requirement that exercise testing be done included in the original protocol were changed by agreement among all of the investigators and did not affect the conclusions of the study. Exhibit A to this letter may be helpful in understanding how patients were evaluated for inclusion in the study.

During the meeting on September 10, 2018, Dr. Rynn agreed to adjust Dr. Jiang's duties on inpatient services to later date so Dr. Jiang would have time to work on responses to the Audit report prior to her fall trip to China. Meanwhile, Dr. Jiang committed to work with her team and department CRU to complete the responses and submitted to Duke IRB prior to her departure to China.

On September 11, 2018, Dr. Rynn requested via email to have a follow-up meeting with Dr. Jiang on September 12, 2018, at 2:30pm, copying Jennifer Ellis and Angela Garrett. Due to schedule conflicts, the meeting was set for September 17, 2018. Dr. Rynn refused to allow the REMIT study manager and statistician, Dr. Steve Boyle, to attend the meeting. When Dr. Jiang learned that Dr. Rynn would not permit her chief statistician on the study attend the meeting, she became worried that the meeting would be another attempt for Dr. Rynn to bully her.

Thus, prior to the meeting, Dr. Jiang reached out to Dr. Ann Brown, Vice Dean for Faculty Development for advice about to handle Dr. Rynn's treatment of Dr. Jiang. After their discussion, Dr. Jiang wrote Dr. Brown thanking for her for the "therapeutic session" and indicating that as a result of their conversation, Dr. Jiang felt less threatened by Dr. Rynn and more able to attempt direct and effective communications with Dr. Rynn. Dr. Brown responded saying: "What a nice outcome! You are an important and senior member of the department-I will be very interested in how things evolve for the situation you mentioned. Ann." Dr. Jiang also reached

out to the Faculty Ombudsman, Dr. Tom Metzloff, about her concerns about Dr. Rynn as well.

The meeting between Dr. Jiang and Dr. Rynn occurred on September 17, 2018, and Dr. Rynn informed Dr. Jiang that Dr. Rynn questioned whether Dr. Jiang had the ability to be a Primary Investigator (PI). Dr. Rynn seemed to completely discount the 2006-2011 time period that Dr. Jiang had served as the PI on the Remit Study or the complicating factors including the transition from paper to electronic documents, the turnover in lab personnel, and the forced relocation of the lab in the middle of the study.

On Sep 18, 2018, Dr. Jiang send an e-mail to Dr. Ann Brown at 1:46 PM revealing the meeting content.

Wei Jiang, M.D. <wei.jiang@duke.edu> wrote:

> Dear Ann,
>
> Dr. R called for a meeting with me yesterday and talked about my ability/capacity of being a PI will be examined and I might be removed from the PI role. Knowing what kind of patterns she has, I am no longer afraid of her. But cannot neglect the negative impact completely. The repeated invalidation, lack of empathy, and threatening talks are extremely disturbing.
>
> I welcome and appreciate any advice you may have.
>
> Best, Jan

In response, Dr. Brown, Tuesday, September 18, 2018 2:46 PM, wrote:

> > Jan- this sounds quite serious. Reading your note, it seems like there is a discrepancy in how each of you understands the problem. And it seems from what you say that she may not appreciate/be convinced of your strong commitment to ethical conduct of research (that is my assumption from reading that she wants to consider removing you from PI role). I hope the discussion with her can clarify that if it is in fact a gap in understanding, and that you can convey what I know is your strong commitment to conducting solid research. This sounds very stressful-Ann

On September 20, 2018, Pamela Bonner, Dr. Jiang's former research coordinator, emailed Dr. Jiang and asked her to serve as a reference for Bonner. Dr. Jiang recalled that Jeannie Beckham had informed Dr. Jiang back in April that Pamela Bonner's complaints about Dr. Jiang's lab practices had precipitated the original departmental

audit and that further, Bonner asked to be transferred from Dr. Jiang's lab, Dr. Jiang then determined that she needed to know the nature of Bonner's previous concerns about Dr. Jiang's lab especially in light of Dr. Rynn's instigation of the initial CRU audit, so Dr. Jiang scheduled a meeting with Bonner, also attended by Dr. Steve Boyle, Dr. Jiang's team statistician and laboratory manager, on September 24, 2018.

At the meeting, Bonner informed Dr. Jiang and Dr. Boyle that back in April 2018, while Dr. Jiang was in China, she was called in to Chair's office and "grilled" by Dr. Rynn for approximately an hour about the work going on in Jiang's lab. Bonner told Dr. Jiang and Dr. Boyle that she never told Dr. Rynn that she had problems with the lab. In addition, Bonner indicated that she had been told by Dr. Rynn not to discuss the meeting with Dr. Jiang. After the meeting, Dr. Jiang confirmed Bonner's statements with her in an email. These new revelations convinced Dr. Jiang that Dr. Rynn had actually instigated the original CRU audit in bad faith while Dr. Jiang was in China and unable to defend herself and that she had essentially attempted to create issues about Dr. Jiang's ability to serve as a PI out of whole cloth.

On September 24, 2018, Dr. Jiang's latest successful grant, the NHLBI project R01, R01HL140060 designed to examine "Mental Stress-Induced Left Ventricular Dysfunction and Mitochondrial Dysfunction in Women" was awarded for a period for 4 years.[7]

Due to Dr. Rynn's hostility towards Dr. Jiang, Dr. Jiang had previous reached out to Tom Metzloff, the Ombudsman, for advice and support on how to deal with the situation. On September 26, 2018, Dr. Jiang reached out to Metzloff again via email and requested his advice regarding Dr. Rynn's repeated threats to her:

> Dr. Rynn has said three times to me since August 20, 2018 (Dr. Beckham has heard all) that she has the power to cancel my new R01 (NHLBI awarded me an R01 in August) twice and that my "ability and capacity for being a PI will have to be re-examined and may not be able to conduct my new study) on September 10, 2018. I have felt being highly threatened by her. That's the reason of me contacting you for advice with the e-mail message from Dr. Swamy.

On September 28, 2018, Dr. Swamy, Associate Dean Clinical Research, held a meeting with Dr. Jiang, Jeannie Beckham, Dr. Rynn, and also with Jen Ellis (Psychiatry vice-chair finance), and Scott Gibson, Executive Vice Dean for Administration for the Duke University School of Medicine. The purpose of the

[7] On November 23, 2018, the study was extended to five years, as requested in Dr. Jiang's original proposal. The initial year alone was funded at almost $800,000.00.

meeting was to discuss tasks that needed to be taken care of for the conclusion of the REMIT audit so Dr. Jiang's team could start the new R01 project sooner than later. There was no mention that the new R01 would be terminated.

On October 2, 2018, Dr. Jiang and Dr. Boyle, her lab manager/statistician, had a meeting with Terry Ainsworth (Duke IRB staff member) and Alifia Hasan (Psychiatry department CRU staff) who were then helping Dr. Jiang from a research regulatory standpoint on responding to the audit. During this meeting, Dr. Jiang, Dr. Boyle, Ainsworth, and Hasan reviewed the response carefully and made changes accordingly. Ainsworth and Hasan offered to finalize the response with Dr. Rynn before submitting to Duke IRB.

On October 3, Dr. Jiang sent her draft of her response to the REMIT Audit report, via e-mail, to Ainsworth and Hasan and also sent it to Dr. Rynn. Dr. Jiang's response to the Audit report was formally submitted to Duke IRB on 10.18.2020 by Dr. Boyle and Hasan. The response fully explained the protocol changes and that no "ineligible" patients were included in the study.

Between October 4, and November 1, 2018, Dr. Jiang was in China on her outreach and family trip.

After Dr. Jiang returned from China, on November 13, 2018, she and Stephen Boyle met with Greg Samsa and Donna Kessler from the Data Integrity Office to discuss process changes recommended. At this meeting, Greg Samsa expressed his opinion that fact that the protocols were not amended was a common issue seen by the Duke Clinical Research Institute (DCRI) when reviewing clinical trials, with the implication being that it was not that serious. Neither Samsa nor Kessler ever indicated to Dr. Jiang or Stephen Boyle that the science behind the REMIT study was not sound.

On November 23, 2018, NHLBI notified Dr. Jiang and Duke that the new R01 would be extended from four to five years.

On December 26, 2018, after having reviewed the Audit Report from the OARC and the response of Dr. Jiang and her team to the Audit Report, the IRB concluded that study deficiencies in protocol identified in the audit did not represent an Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO). The IRB noted that it agreed with the audit recommendations and that the IRB was forwarding the matter to the Institutional Official, Dean of the School of Medicine Mary Klotman, for her final determination. In addition, the internal IRB Outcome indicated that it needed "to see expert opinion, independent of the study team, on the interpretation of the stress tests, ECHOs and how the ineligible patients

were handled in reporting the data" before it could make a final determination and asked the PI (Dr. Jiang) and Investigators, with the support of the CRU and School of Medicine, to seek "an independent expert opinion on these issues and report back to the Board with their conclusions."

In response to the IRB outcome, the Department apparently decided to issue another CRU report dated January 7, 2019, which focused primarily on: (1) documenting eligibility criteria of all randomized participants and (2) comparing collected data to the IRB approved protocol and informed consent form (ICF). In this report, Terry Ainsworth, Director of Research Operations (DOCR), Alifia Hasan, RPM, Psychiatry CRU, and Scott Compton, Director of Psychiatry CRU, reported their additional findings regarding the eligibility of certain randomized participants in the REMIT study and comparing the collected data to the IRM approved protocol and informed consent forms.

It is critical to note that there is no debate about whether participants in the REMIT study were allowed to continue regardless of whether they had discontinued beta blocking medication prior to the stress testing or were able to perform exercise testing. The original **exclusion** (not **inclusion** labelled in the 01.07.2019 report) criteria were amended during the study in consideration of participants' safety and given that having patients' data from the exercise test was not the primary goal of the study. Thus, the elimination of the exercise test for some individual subjects (along with the elimination of the requirement that beta blockers be withheld) was not a reportable issue to the IRB; it enhanced patient safety and had no effect on the data integrity.

Moreover, these subjects of the **second** CRU department audit were not new issues; they had previously been identified in the **first** CRU department audit and addressed then. Moreover, they had also been noted in the OARC audit report and Dr. Jiang had explained in response to both that the eligibility criteria were changed **to ensure patient safety** and that the **revised criteria did not affect the scientific conclusions of the study**.

In addition, the second CRU audit concluded that "protocol violations" occurred: These purported "violations" were without basis as seen below:

"Violation"	**Response**
Protocol does not state that data from non-participating patients will be used in publications.	The participants who provided informed consent were the 307 patients who provided information consent and were provided a schedule

	of assessments and told that their data would be used in publications. These participants were included in the Repository study; only 127 were included in the primary drug/placebo study. **All publications have only used data from patients who participated in and provided informed consent for both of the the REMIT studies.**
Informed Consent Form (ICF) does not state that data from non-participating patients will be used in publications.	Data was collected from participating patients in the REMIT RCT (N=307). **The publications have only used data from participating patients in both of the REMIT studies.**
2017 publication reported longitudinal findings for a median of four years.	**The publications have only used data from patients who participated in both of the REMIT studies**
The publication states that the study protocol was not approved by the IRB and participants provided written informed consent.	**The study protocol was in fact approved by the IRB. The participating patients did in fact provided written informed consent in both of the REMIT studies.**
The ICF contains a schedule of events or assessments only for participants in the REMIT RCT.	**The publications have only used data from patients who participated in and provided informed consent for both of the REMIT studies.**

Also, on January 7, 2019, Dr. Jiang met with Jeannie Beckham and Dr. Rynn to discuss the challenge of implementing the new R01 in psychiatry because the research project was multi-disciplinary and was primarily a cardiovascular research project. Dr. Jiang suggested that it might be better to move the CRU oversight of the new R01 project to the Medicine department. Dr. Rynn again reminded Dr. Jiang that she was the Department Chair and had the power to terminate the new R01.[8]

In addition, on that same date, Dr. Jiang initiated discussions with Dr. Rynn and others in response to the IRB request that it wanted "to see expert opinion, independent of the study team, on the interpretation of the stress tests, ECHOs and how the ineligible patients were handled in reporting the data" before it could make a final determination and ***asked the PI (Dr. Jiang) and Investigators, with the support of the CRU and School of Medicine***, to seek "an independent expert opinion on these issues and report back to the Board with their conclusions."

Specifically, Dr. Jiang met with Scott Compton, Director of the Clinical Research Unit (CRU) and Alifia Hasan, Research Practice Manager on Monday, January 7 to discuss the details of the IRB's request for additional data. On Wednesday, January 9, Compton sent an email to Dr. Jiang, copied to Alifia Hasan, Research Practice Manager, Cameron Howes, Assistant Research Practice Manager, Dr. Rynn, and Jennifer Ellis, the Study Coordinator, which stated the following:

> Just to close the loop regarding one question you raised at our face-to-face meeting on Monday. At that time I mentioned that I would talk to Jody Power, director of the IRB, about whether we needed to re-rate all exercise stress tests and ECHOs or just a random sample. I was able to reach Jody and she said that at this point, a random sample would be okay. She made it clear to me that this would be a start and that they might require an additional "deeper dive" at some point. So for now, we are going to organize a 20% random sample of these tests for re-rating, provide a report back to the IRB of our findings, and the await further instructions.

Dr. Jiang then responded and indicated that she was going to forward the message regarding random sample along with the IRB outcome letter to the cardiologists who

[8] Dr. Rynn actually made this statement to Dr. Jiang on four separate occasions prior to January 25, 2019. Dr. Beckham also stated the same thing to were ongoing between Dr. Rynn and Beckham planned to do exactly that.

were the REMIT co-investigators for their response. Scott Compton then replied to Dr. Jiang stating:

> I believe you mentioned that these people are no longer at Duke. Correct? If so, please remember that Moira expressly asked that we not discuss the audit with anyone outside of Duke. In fact, she requested that we not discuss this issue with anyone outside of those who attended our meeting. Based upon this request, I think it would not be prudent to inform the cardiologists at this point in time.

Dr. Rynn then followed up stating:

> That is correct, Scott, no one has my permission to share any information pertaining to this audit outside of our group. Thanks, Moira

Uncertain how to provide the IRB with the requested information without contacting her cardiology co-investigators, Dr. Jiang then wrote back to Dr. Rynn and Scott Compton:

> Dear Moira and Scott,
>
> I hear from you regarding not discussing the audit outside of this group. I would highly appreciate you sharing with me the rationale(s) behind it since I am having a hard time comprehending why I cannot communicate with the co-investigators of REMIT about the audit. They have been working with us for many years and have made unique contributions to REMIT study. From the Echo standpoint, as the PI of REMIT, except for outlining guidelines, I have no role in the REMIT echo quality and interpretation process. I feel that it would be respectful to my echo-cardiology collaborative colleagues, who reviewed all the REMIT echo images, that their echo ratings will be re-examined. Dr. Eric Velazquez and Dr. Zainab Samad are very well known echo-cardiologists who have had top level echo training. They also have enriched experience in analyzing mental stress induced cardiac echo images. I think they may have adjunct positions with Duke after they moved to Chairs of Medicine in different institutions. I sincerely think they need to be informed of the decision to re-read the echo images.
>
> Moving forward, I would like to make a suggestion. Given the nature of cardiac echo imaging study and the unique hemodynamic impact of mental stress on cardiovascular system, it would be a good idea to have echo-cardiologists who have had comparable training and experience with mental stress testing to do the required re-rating.

Not surprisingly, Dr. Jiang received no response or follow up to this email from either Compton or Rynn. In fact, Dr. Rynn ultimately procured review by untrained cardiologists to re-read the echocardiograms.

Dr. Jiang's attempt to resist and escape Dr. Rynn's discriminatory treatment of Dr. Jiang by moving oversight of the new grant out of Psychiatry and into Medicine (Cardiology) was then met with an unprecedented and completely retaliatory action by Dr. Rynn. **Inexplicably, but not unexpectedly, given the previous and repeated threats made to Dr. Jiang, on January 23, 2019, Dr. Rynn and Dr. Swamy held a meeting with Dr. Jiang and informed her that Dr. Jiang's new R01 would be terminated.**

In fact, IRB policies do not give Dr. Rynn the power to terminate a grant previously approved by the IRB. The IRB policy specifically defines a "termination" as "[a]n action by the convened IRB to stop permanently all activities of a previously approved research protocol. Terminated protocols are closed protocols, and they no longer require continuing review." Dr. Jiang's research grant had an IRB approved protocol at the time of Dr. Rynn's termination.

The policy then provides the following procedures for both the "Immediate Suspension or Termination of IRB Approval by an IRB Chair, Executive Director, or the IO (Institutional Official) or his/her Designee" and for the "Suspension of Termination of IRB Approval by the Convened IRB." Specifically:

> **2. Immediate Suspension or Termination of IRB Approval by an IRB Chair, Executive Director, or the IO[9] or his/her Designee**
>
> - The Chair, Executive Director, or the IO or his/her designee (collectively, "Reviewer") considers whether any immediate actions are needed to protect the safety, rights and welfare of current subjects or to eliminate an apparent hazard.
> - The Reviewer documents with the IRB the reasons for the suspension and any actions taken.
> - The Reviewer communicates this information to the PI.
> - The IRB Specialist places the suspension or termination on the agenda of the next available IRB meeting:
>   - o The convened IRB votes to continue, reverse or modify the suspension or termination.

[9] As stated above, Dean Mary Klotman of the Duke University School of Medicine has been designated as the Institutional Official for the Duke University Health System (DUHS) Human Research Protection Program.

- If the IRB votes to continue or modify the suspension or termination, the procedure described below in item 3 is used.

3. Suspension or Termination of IRB Approval by the Convened IRB

- The IRB considers whether any action is needed to protect the safety, rights and welfare of current subjects.
- Actions might include:
  - Transferring subjects to another PI
  - Making arrangements for clinical care outside of the research
  - Allowing continuation of some research activities under the supervision of an independent monitor
  - Notification of current subjects
  - Notification of former subjects
  - For terminated studies:
    - Requiring or permitting follow-up of subjects for safety reasons
    - Requiring adverse events or outcomes to be reported to the IRB and the sponsor.
- The IRB documents in the IRB minutes the reason for the suspension, and if applicable, any actions taken.
- The IRB Chair, working with the IRB Specialist and Executive Director, communicates these findings to the PI, the IO, appropriate institutional officials, and any applicable funding or regulatory agencies.

Clearly, this policy was not followed when Dr. Rynn unilaterally terminated Dr. Jiang's grant.

Dr. Jiang is informed and believes that the act of relinquishing a funded NIH grant is a monumental event that has never occurred in Psychiatry department, if ever at Duke University at all. Dr. Rynn refused to provide Dr. Jiang with any reason for the relinquishment, except for her repeated statements that she was the Chair and had the power to stop it. Dr. Jiang expressed her desire to have more detail on reason(s) for the termination of the grant. Dr. Swamy told Dr. Jiang that she'd compose a letter to NHLBI for the termination and would share the letter with Dr. Jiang prior to submitting it to the NIH system. Dr. Jiang never received such a letter or notification. This action by Dr. Rynn resulted in the loss of first year funds alone of almost $800,000.00.

The facts clearly support that this completely unwarranted, discriminatory, and retaliatory action was undertaken by Dr. Rynn who acted with racial/ethnic/gender/age bias against Dr. Jiang who was more successful professionally and academically than Dr. Rynn and and who was also clearly a talented and cutting edge clinical researcher. At the very least, Dr. Rynn acted with improper personal malice and in a matter inconsistent with professionalism and academic integrity.

Dr. Rynn's termination of Dr. Jiang's new R01 negatively impacted the professional career of Dr. Jiang and several of her colleagues, Dr. Jiang's professional reputation, and significantly Dr. Jiang's financial support, given that 30-50% of Dr. Jiang's university salary would have been covered for at least five years by this grant. Furthermore, Dr. Rynn cut the line of the successfully ongoing neuro-psycho-cardiology research that if pursued, would have brought significant and valuable knowledge to human health and provided cutting edge research to which many were looking forward. Finally, the new R01 was going to bring multiple smaller grants since the study area of the grant would have been extremely innovative and much new knowledge could have been uncovered from the line of investigation in the study.

Not content to sabotage Dr. Jiang's previous and then pending research career, Dr. Rynn then attempted to curtain Dr. Jiang's global mental health outreach in China. Dr. Jiang knew from other faculty members that Dr. Rynn had no interest in supporting global health activities and Dr. Rynn informed Dr. Jiang directly that Global Health is not her interest.[10]

At some point prior to February 22, 2019, Dr. Rynn informed Dr. Jiang that she would not be permitted to take her April trip to China due to the need for her to stay at Duke in case she needed to address issues emerging from the audit. Dr. Rynn maintained this position even though the CRU director told Dr. Jiang that any issues could be addressed electronically.

On February 22, 2019, Dr. Jiang wrote Dr. Rynn and requested that she reconsider her position:

> Dear Moira,

[10] In fact, after Dr. Rynn's successful termination of Dr. Jiang's new research project, Dr. Jiang was offered salary and overhead by some of her health care collaborators in China but Dr. Rynn refused to acknowledge the offer or accept it.

> I sincerely hope you may reconsider my request to visit China in April 2019.
>
> I fully recognize the significance and seriousness of the REMIT audit and have promptly responded to questions coming from the IRB and other offices managing this audit. Based on requirements of the audit so far and what may come in down the road, Scott, Steve, and I all think, if there is some urgent request during the time I am travelling, we can still respond promptly and effectively. There will be no delay due to the travel.
>
> I established my academic commitment to China in 2003. I have set up two primary goals to achieve in China this year, one is to enhance the understanding and resolving the fear and fear related symptoms emerging from significant physical events, and the other is to make the team approach in health provision more comprehensive and accepted in medical practice in China. You may find the topic of my formal talk in the April international CV conference (Formal invitation attached) of interest. I have also attached for you a brief description of why implementing mental health and integrated care is particularly important.
>
> To accommodate your requirements, I am willing to reduce my trip to no more than 10 work-days and have also taken an extra week of inpatient service in April 2019. I highly appreciate your re-consideration and approval of my trip to China, so I can have an uninterrupted academic practice there.
>
> Sincerely,
>
> Jan

On February 24, 2019, Dr. Rynn replied:

> Hi Jan,
>
> Let's set up a time to meet. There is a clinical matter I would like to discuss with you and also would like to review your academic and clinical financial support.
>
> Thanks, Moira

The meeting was scheduled for March 1, 2019. Concerned about the meeting, Dr. Jiang sought to have Dr. Tom Metzloff, the Duke Faculty Ombudsman, present at

the meeting. At the beginning of the meeting, Dr. Rynn requested to talk to Dr. Jiang and Dr. Ellis, without the Ombudsman, presumably for HIPAA reasons related to patient confidentiality, about a concern on an event that happened with the Psychiatry consult service regarding a patient. Dr. Rynn then proceeded to accuse Dr. Jiang of refusing to see a patient on a psychiatry consult. In fact, Dr. Jiang declined the psychiatric consult on the patient who was with the Surgical ICU (Intensive care unit) for completely appropriate reasons which she explained to Dr. Rynn. After finishing the discussion of the patient issue, Dr. Rynn then permitted Dr. Metzloff, the Ombudsman, to enter the meeting with Dr. Rynn, Dr. Jiang, and Jen Ellis to discuss Dr. Jiang's request to visit China in April 2019.

The remainder of the meeting, about 40 minutes, involved Dr. Rynn reiterating that for Dr. Jiang's sake, she could not allow Dr. Jiang to leave Duke Campus because Jiang might need to respond questions about the REMIT study. During the meeting, Dr. Rynn became more and more restless and irritable when Dr. Metzloff and Dr. Jiang offered that the department CRU director Scott Compton had indicated that Dr. Jiang could respond via electronic communication. At one point, Dr. Rynn accused Dr. Jiang of being too calm, and stated that if she were Dr. Jiang, she would be anxiously staying at Duke, not going anywhere else, while awaiting the results of the Audit.

Due to the meeting with the Ombudsman and Dr. Rynn on March 1, 2019, Dr. Jiang cancelled the trip, following the suggestion of the Ombudsman who felt that it might ease the obviously hostile behavior Dr. Rynn had demonstrated toward Dr. Jiang. As anticipated, there was no face-to-face interaction required to address questions about the study during this period, which meant that Dr. Jiang could actually have gone to China without any negative impact on the REMIT audit. It also meant that Dr. Rynn had successfully intimidated Dr. Jiang once again, and continued her discriminatory and retaliatory treatment of Dr. Jiang.

Not content to have cancelled Dr. Jiang's five year research grant with a first year value of almost $800,000, and to have successfully caused Dr. Jiang to cancel her outreach trip to China, on March 4,unbeknownst to Dr. Jiang at the time, Dr. Rynn or someone at her direction communicated potentially libelous or slanderous, but certainly derogatory and misleading information, to the U.S. Department of Health and Human Services (DHHS) which information was sufficient to result in the instigation of an investigation into whether Dr. Jiang engaged in ***professional misconduct*** for the same study that was the subject of the internal audits instigated by Dr. Rynn. This further escalation of Dr. Rynn's attempt to essentially ruin Dr. Jiang's research career had reached new heights.

In fact, on March 4, after having received allegations of professional misconduct relating to the REMIT study, the NIH Research Integrity Officer (RIO) provided information to the US DHHS Office of Research Integrity (ORI) Director of Investigative Oversight (DIO) about the RIO's receipt of notification of allegations of possible falsification of the clinical research record for the Responses of Myocardial Ischemia to Escitalopram Treatment (REMIT) clinical research study. On that same date, the ORI sent a letter to Duke requesting an inquiry be conducted.

On March 6, an email was sent from Michael Dickman with the Duke Office of Research Administration to Christina Rinaldi, NIH representing that Duke University wished to relinquish the funds associated with the new five year grant awarded to Dr. Jiang. On that same date, the remaining funds for the first year of the public health service research grant terminated by Dr. Rynn ($799,690.00) were returned to US DHHS, Public Health Service.

Notably, and not shared with Dr. Jiang at the time, Susanna Stevens and Lilin She reported the results of their REMIT trial re-analysis work via email on March 8, 2019. The email from Dr. She stated:

> As the first step, Susanna and I have tried to replicate a few key numbers for the primary results published in JAMA using the same patient population and the same datasets and programs sent to DCRI. We can replicate some of the numbers, but cannot replicate some others. Overall, our numbers are very close to what were published. If we have more time, we would like to investigate further on why we could not match 100% with the JAMA paper.
>
> As the second step, we also rerun the SAS programs after excluding those 26 subjects who are considered as not eligible[11] according to the recent assessment. The results are slightly changed. You can review the differences in the attached tables. Since we now have a smaller sample size, the p-values are changed. However, the results obtained from this reduced patient sample are in general very similar to the results published in JAMA.

On March 11, 2019, Dr. Jiang received an email from Donna Kessler, Research Integrity Officer, notifying her of the request from the Health and Human Services (HHS) Office of Research Integrity (ORI) to conduct an inquiry into allegations of possible falsification of the REMIT clinical research records which would constitute

[11] It is not clear who made the determination that 26 subjects were considered "not eligible" and on what grounds. Nonetheless, even with the reduced patient sample, She reported that the results were "very similar to the results published in JAMA."

professional misconduct. The purpose of the inquiry was to determine if there was evidence of potential research misconduct that would warrant further investigation. The email also stated that the inquiry would be conducted by members of the Duke Standing Committee on Misconduct in Research (SCMR).

On March 25, 2019, the SCMR initiated a re-evaluation (re-reads) of echocardiograms from the REMIT study by Dr. Pam Douglas with the Duke Clinical Research Institute. On April 11, 2019, the SCMR initiated a statistical re-analysis of the primary REMIT study outcomes provided in the 2013 JAMA publication of the study results.

Despite being told that Dr. Rynn had terminated her grant, Dr. Jiang continued to receive messages from the NHLBI concerning her need to complete activities consistent with the grant being active. To address these emails, on April 19, 2019, Dr. Jiang wrote to Dr. Swamy, who had indicated previously on January 23, 2019, that she would provide Dr. Jiang with correspondence to NIH regarding the termination of the grant.

> Dear Dr. Swamy,
>
> May you please verify the relinquishment of my new R01(R01 HL140060 for us? I have not seen the letter or report to NIH that you said you would share with me during our meeting on 01/23/19. Dr. Compton, the Psychiatry department CRU director, has verbally informed me that the termination of the R01 has been formal. However, I continue receiving notifications from NHLBI regarding activities that I, the PI of the project, need to address, and reminder that I am late in responding to those requirements. I did not respond because I have been following the guidance of our CRU that we not communicate with NHLBI regarding this matter.
>
> I view having a formal notification of the R01 relinquishment is necessary for our record keeping.
>
> Best, Jan

Significantly, Dr. Swamy replied on April 25, 2019:

> Jan,
>
> Thank you for your email and my apologies in not responding to you sooner. Please see the attached documentation that Duke has relinquished the grant. As we discussed previously and is stated in the Duke Faculty Handbook (appendix P, page 41), faculty are not permitted

> to communicate with external sponsors on administrative issues. We also discussed that you would like to speak with your program officer, Catherine Stoney, about your continued interest in the research from a scientific perspective. ***You may do that but only with someone from your department/CRU leadership or School of Medicine Leadership included on the phone call with you.*** I have copied Scott and Moira on this email so that you may work with them to determine next steps and who to include on such a call if you would like to proceed with that plan.
>
> Thanks,
>
> Geeta

This email both provided Dr. Jiang with no documentation regarding Dr. Rynn's cancellation of her grant, but also with further evidence of Dr. Rynn's attempts, through Dr. Swarmy, to continue Dr. Rynn's efforts to insulate Dr. Jiang from having any contact with anyone who could question or oppose Dr. Rynn's discriminatory and retaliatory treatment of Dr. Jiang. Dr. Jiang learned that on March 6, 2019, Michael Dickman sent an email to Christina Rinaldi at the NIH/NHLBI stated that the University wanted to "initiate the process" for relinquishing the ***first year budget award*** of $799,690.00 to the U.S. Department of Health and Human Services, Public Health Service 1R01-HL140060-01A1, and actually accomplish that on same date.

The Duke Standing Committee on Misconduct in Research Committee (SCMR) interviewed Dr. Stephen Boyle, Dr. Jiang's co-author on the REMIT study publications, on May 21, 2019. Dr. Jiang was interviewed by the Committee on June 17, 2019. On July 15, the SCMR interviewed Jennifer Wilson, who had served as one of the REMIT Study coordinators; there were several, including Pamela Bonner.

On July 12, 2019, Dr. Jiang received an email announcing a School of Medicine/Duke Health position for Assistant Director positions to work with the new Center for Interprofessional Education and Care which was created to expand opportunities for learners and clinicians throughout the health system to enhance their skills in interprofessional practice, working with the Center Director Mitch Heflin, and focusing on the areas of preclinical and clinical education, faculty development, evaluation and scholarship. The announcement also indicated that applications required a cover letter summarizing interest, a copy of the applicant's curriculum vitae, and most significantly for Dr. Jiang, a letter of support from the applicant's department chair, division or program head, attesting to the applicant's qualifications and their support for the applicant's time, which was estimated to be one day a week.

Dr. Jiang reached out on July 15 to Jeannie Beckham and Dr. Rynn regarding Dr. Jiang's interest in the position and asking for their support for her application. Dr. Jiang also reached out on July 16 by email to Dr. Heflin, the Center Director and expressed her interest and asked whether there were funds available to cover the time spent in the position because her chief wanted to know. Dr. Heflin replied that there were funds available. Dr. Rynn did not respond to Dr. Jiang's email until July 23 and then indicated that she wanted to set up a meeting to discuss the matter of Dr. Jiang's application.

Dr. Jiang met with Dr. Rynn and Jean Beckham on DATE. On July 31, 2019, Dr. Jiang wrote an email to Dr. Rynn to summarize the discussions at the meeting which included both Dr. Jiang's proposed Fall trip to China and the School of Medicine position

> Dear Moira,
>
> Thank you for taking time to meet me.
>
> I would like to summarize what I have learned from you at the meeting.
>
> 1. Re: My application request to response to the call of the Duke IPEC
>
> I heard from you that you have reached out to the Duke IPEC and learned that the program is looking for individuals who have had a high volume of outpatient services. Such individual will be in leadership of leading IP outpatient service. You have discussed with Dr. Shirey (may be others that I could not recall names) and made your nominations to IPEC. You will not make any new nominations for the AD position of the Duke IPEC. It is your opinion that I am not at the level of the IPEC is looking for.
>
> 2. My visit to my mother in China in the fall
>
> You gave me your support for it, provided that I work out with Dr. Holmer for not having conflict on inpatient service.
>
> Best,
>
> Jan

Dr. Rynn then responded to Dr. Jiang's email:

> Yes, reached out to SOM and Drs. Holmer and Heilbron for appropriate nominations who stressed the importance of leadership experience of an multi-discipline professional team and strong communication skills.
>
> And if we could please have your vacation dates that you plan to take.
>
> Thanks, Moira

Because Dr. Rynn refused to support Dr. Jiang's application for the position, Dr. Jiang then reached out to Dr. Heflin to communicate Dr. Rynn's decision not to support Dr. Jiang's application.

> Dr. Rynn informed me that she has reached out to SOM and Drs. Holmer (Psychiatry inpatient service director) and Heilbron (Psychiatry department vice Chair for clinics) for appropriate nominations who stressed the importance of leadership experience of an multi-discipline professional team and strong communication skills. Dr. Rynn learned that your IPEC program is looking for individuals who have had a high volume of outpatient services. Such individual will be in leadership of leading IP outpatient service. Dr. Rynn has made her nominations to IPEC and will not make any new nominations for the AD position of the Duke IPEC. Dr. Rynn thinks I am not at the level of the IPEC is looking for.
>
> Best, Jan

Dr. Heflin replied that Dr. Rynn was mistaken that there was a preference for individuals with a high volume of outpatient services and that he would be happy to answer any questions for Dr. Rynn. Dr. Jiang considered whether it would be worthwhile for Dr. Heflin to reach out to Dr. Rynn but decided against doing so as it was clear to Dr. Jiang that Dr. Rynn would not support her no matter. Feeling discouraged and victimized by Dr. Rynn's bullying over the months since the audit commenced and Dr. Rynn unilaterally cancelled her five year grant, Dr. Jiang engaged in introspection about the matter and determined to pose a direct inquiry to Dr. Rynn about Dr. Jiang's status at Duke.

To that end, on August 2, 2019, Dr. Jiang sent the following email with the subject line "clarification appreciated" to Dr. Rynn:

> Dear Moira,
>
> In thinking about our recent conversations, it appears that my role as a tenured, full Professor in our Department has changed significantly over

the past year. I need you to clarify your position regarding several recurring issues that we have discussed over the past several months:

1. My research activities: It is my understanding that you have forbid[den] me from conducting any research in which I am a principal investigator. This restriction includes my examining data from previous studies, writing manuscripts, and applying for new funding from the NIH, industry, or other funding sources. Am I correct that this is your position, and if it is, when can I expect this restriction to be lifted?

2. My international collaborations: It is my understanding that you are not permitting me to pursue my ongoing collaborations with my longtime Chinese colleagues, including not allowing me to travel to China or developing a formal contract with academic centers in China. If this is correct, please provide me with an explanation for your position and an indication of under what circumstances will this restriction be lifted.

3. My professional activities: It is my understanding that you want to limit my professional activities to the inpatient service and to supervise and train residents and medical students on the inpatient service. Is this correct?

4. My new R-01 grant that's relinquished: It was my understanding at the meeting with you and Dr. Swamy that Dr. Swamy planned to compose a letter to NHLBI with reason(s) for the relinquishment. She would share the letter with me prior to communicate with NHLBI for the action. You did not think that was what Dr. Swamy meant.

To make sure there is no misunderstanding, I would appreciate your confirming that this is how you have defined my role in the Department at this time and what I can expect going forward.

Thank you for taking the time to respond to my request.

Sincerely,

Wei Jiang

A week later, on August 9, Dr. Rynn responded, copying Jennifer Ellis, Scott Compton, and Jean Beckham, none of whom were included on Dr. Jiang's original email.

Dear Jan,

Thank you for your most recent email, although I will say that I was surprised to again see questions listed that we have provided answers to in multiple previous communications.

To summarize, the research audit that remains underway regarding your studies is a serious matter and we appreciate your attention and full participation with of our colleagues in the School of Medicine who are working on our behalf to understand and guide us through the next steps. ***At this time, as the audits are underway I am putting your approved research activities on hold, to include the submission of new awards.*** The findings to date clearly outline the need for additional training and resources to enable you to begin to work in research at the highest level of integrity and quality. As a senior faculty member and PI, I expect you to understand and recognize the importance of this support that the Department is providing to you at this time. I also remind you that the NIH and other federal agencies hold Duke – as well as the PI – responsible for adherence to quality.

The expectations for a senior level hospitalist provider are clear and consistent across our PDC provider group. I do understand you are scheduled to work and support patient care services across Duke Health inpatient services this fiscal year. In addition, again consistent with our training programs within the Department of Psychiatry, providers are expected and encouraged to work/teach trainees of all levels in their specific work setting.

Lastly Jan, I do understand that this has been a terribly stressful time and I will again share that the senior leadership team for Research and the Chair's office, along with our partners across the School of Medicine, are working in your long term interest as we take the necessary steps to demonstrate your ability to conduct quality research.

I do not at this time approve professional requests for extended travel that takes you from our clinical operational needs here at Duke, as well as the audit process related to your research program.

All faculty have the same access to vacation and extended leave requests in accordance with the faculty handbook, https://provost.duke.edu/sites/all/files/FHB.pdf. According to the handbook, faculty with twelve-month appointments in the Medical Center have compensation that covers eleven months of effort and one

> month of paid vacation. One month of paid vacation is equal to 22 business days and PDC vacation policy. Please review these resources to determine any further leave at this time. Division Director approval is required for any extended leave related to FMLA etc.
>
> Thanks again Jan for your continued participation in the research inquiry and follow-up. We appreciate all that you do to support our patients and trainees across our inpatient services. We will continue to be in touch regarding feedback on research review.
>
> Moira

Notably, Dr. Rynn did not provide any answers to when the research limitations would be lifted, when the international collaboration restrictions would be lifted, why Dr. Jiang's activities were limited to inpatient services, including teaching, and any questions about the relinquishment of the Dr. Jiang's five year grant. Again, Dr. Jiang felt stone-walled by Dr. Rynn and her refusal to discuss Dr. Jiang's professional activities. Dr. Rynn again declined to provide a reason for terminating Dr. Jiang's new R01 NHLBI grant.

On September 12, 2019, Dr. Jiang was able to meet with Paul Lantos, Jody Power, and Walter Lee, members of the Duke IRB, to discuss Dr. Jiang's concerns regarding the SCMR's draft conclusions and the factual basis for them, specifically with the data included in Appendices E and H (the statistical analysis which omitted the allegedly "ineligible" subjects and Appendices I and J (the analysis of the echocardiograms re-read by Pam Douglas, M.D.). At the meeting, Jody Power, Duke IRB Chair, denied making any comment about needing to "dive deeper" (in REMIT) to Scott Compton or anyone.[12]

Dr. Jiang sent a follow up email after the September 12, 2019 meeting on September 30, thanking them for meeting and inquiring about the IRB summary of the SCMR inquiry. Dr. Lantos responded on October 6 and confirmed understanding of Dr. Jiang's concerns about the application of principles recently developed to work done during the REMIT study. Significantly, he assured Dr. Jiang that they would not "reevaluate 2006 science using 2019 eyes."

> Hi Jan,
>
> Thanks again for coming over to meet us. We certainly heard and acknowledge your concern about whether a reevaluation of the echo data

[12] Scott Compton had reported this remark by Jody Power in an email to Dr. Rynn and Dr. Jiang on January 9, 2019.

> from the REMIT study might cast doubt on your findings primarily due to advances in echocardiography in the years since REMIT was done.
>
> We hopefully provided some reassurance that this would be an unlikely outcome, as our goal is not to reevaluate 2006 science using 2019 eyes. There is really a spectrum of outcomes, with the extremes being that an audit fully confirms the original findings or it's completely incompatible with them. In between these two there could certainly be a gray area in which the original findings would be seen as reasonable. If it happens that the audit finds major fault with the original findings, I can't imagine that this would lead to a summary judgment or action without first diving deeper into these findings, and certainly making sure you and your collaborators aware.
>
> I believe that was the understanding we reached during the meeting. Please let me know if there is anything you believe I missed.

Dr. Jiang wrote back and thanked him and expressed encouragement. She also expressed that the audit had been ongoing for over a year and that she had been forbidden to publish manuscripts or doing research and she had been prevented from sharing her thoughts and concerns about the audit.

> Dear Paul,
>
> Thank you very much for your message summarizing the key element we discussed during our meeting. I am particularly impressed by your comment that "our goal is not to reevaluate 2006 science using 2019 eyes". My perception for the "Our" is that it means Duke IRB. Please clarify if my perception is wrong.
>
> I am much encouraged and confident now regarding the continued REMIT audit that has been happening for more than a year, and remains being open ended. With it, I have been forbidden to publish several manuscripts produced from the REMIT biomarker study, and been forbidden from doing research as PI. I have not given any permission to share my thoughts/concerns for certain issues in the REMIT audit.
>
> I would like to ask you all to provide me update, if possible, on what further evaluation you are doing before I receive the final conclusion of the REMIT audit.
>
> Sincerely,

Best, Jan

In October, another opportunity involving executive leadership in academic medicine (ELAM) became posted and once again Dr. Jiang discussed with her chair, Dr. Rynn, and sought her support per the October 14, 2019 announcement. In a curt, one sentence response, Dr. Rynn replied: At this point in time I am unable to support your application for this program. Dr Jiang sought an explanation: " That's disappointing. I'd highly appreciate if you may provide me the reason(s) underlying your decision. Jan" the same day and again, Dr. Rynn's reply was curt and lacked any substantive information: "It is based upon the issues we have already discussed."

On October 22, 2019, the Duke Standing Committee on Research Misconduct (SCRM) was issued and concluded that there was no evidence of falsification or fabrication of study records. The report again noted that the beta blocker and exercise stress testing amendments form the original protocol and again alleged they were not communicated to the IRB as required. But significantly, no new information was provided by the SCRM inquiry. Appendices A – K accompanied the review.

As previously found in the departmental audit and the OARC audit, Dr. Jiang's focus on the study was not the exercise testing originally included as one of the three aims of the study. Dr. Jiang's focus was on the evaluation of escitalopram versus placebo on the mental stress-induced myocardial ischemia (MSIMI) in patients with stable ischemic heart disease (IHD). The study also examined the effects of escitalopram on depression symptoms, platelet activity and cardiovascular stress response in relationship to MSIMI. (Duke OARC Report September 12, 2018, p 2).

Moreover, the SCMR noted that "protocol deviations were readily apparent in the study records" and resulted from "an inconsistency between Dr. Jiang's view of the purpose of the study and the description of the study in the [original] protocol." Again, as previously concluded, the "failings" resulted from the "unamended" IRB protocols. Other data disorganization also likely resulted from the turnover of the study staff and limited funding available for the study to both hire and train study personnel, as well as the transition from paper to electronic records, the physical relocation of the study, and the changes over time in clinical research protocols in place at the University, most notable beginning in 2012, after the REMIT primary study ended in 2011.

Notably, the SCRM report contained a section labelled "Assessment of Facts." In reality, the "Assessment of Facts" contained both facts and conclusions based on facts as well as unsupported opinion evidence. A summary of the questionable "facts" found by the SCMR is contained in Exhibit B to this letter.

Of specific concern, however, to Dr. Jiang were the "facts" related to the re-reading of the echocardiograms contained in numbers 9 and 12. The only additional findings of any possible import were the evaluations by Pam Douglas, M.D. who was selected by the Psychiatry Department to perform a re-reading of the echocardiograms for certain participants in the REMIT study for the DCRI (Duke Clinical Research Institute) and relied upon by the SCRM in its report.

It should be noted that in December 2018, the IRB placed the responsibility for obtaining the "independent evaluation" of the echocardiograms explicitly on Dr. Jiang, as the principal investigator, and her co-investigators, Dr. O'Connor, Dr. Velazquez, and Dr. Samad, to obtain "independent expert opinion on these issues and report back to the Board with their conclusion." Instead, Dr. Jiang and her co-investigators were completely cut out of the process and Dr. Douglas was selected presumably by Dr. Rynn or others at her behest to do the analysis. Dr. Jiang, and Drs O'Connor, Velazquez, and Samad all are of the opinion that the re-evaluation of the echocardiograms by Dr. Douglas was flawed and Dr. Jiang raised this issue with Donna Kessler prior to the release date of the report on October 22, 2019.

In the report Dr. Douglas stated, without explanation, in Appendix I that "the study design with respect to collecting and analyzing echocardiograms for MSIMI determinations (which is the central focus of the REMIT study) was ***not optimal***[13] and contributed to the difficulty of reproducing the findings," which statement was adopted by the SCRM as a "fact." In reality, this conclusion was not the result of "independent cardiologists" as stated in the SCRM "facts" but by one cardiologist, Dr. Douglas. Dr. Douglas' impartiality and expertise are subject to question due to her lack of expertise in mental stress testing and mental stress induced myocardial ischemia. This area of inquiry was the subject of the REMIT study and was considered state of the art research. Moreover, if Dr. Douglas lacked information and training in this field, her reading of REMIT echo images would have been negatively affected by the same.

In fact, the two echo-cardiologists who analyzed the REMIT echo images originally had been trained on how to analyze REMIT echo images. In addition, they analyzed all the images consensually whereas Dr. Douglas only re-read a proportion of REMIT echo images for unclear reasons, and there is no indication that she read the images in consultation with any colleagues, and certainly not with any colleagues trained in this area. Finally, Dr. Douglas provided no explanation as to how she produced the EF scores she included in her evaluation. In fact, the echo-cardiology lab which did

[13] No detail was provided either in the SCRM report or otherwise about how the study design could have been more "**optimal.**"

the original reading used software to analyze the REMIT echo images and produce the original EF scores and the REMIT cardiologists validated these measurements.

As for the actual design of the study which Dr. Douglas criticized, in fact, the REMIT study was designed between 2003 and 2006 and used the best methods at that time relating to when and how the echocardiogram should be utilized in mental stress and exercise stress testing. Dr. Douglas' evaluation in March 2019 imposed her opinion of 2019 design standards on a study designed more than ten years prior.

Finally, Dr. Douglas failed to perform a thorough evaluation on the REMIT echo images in that she did not re-read for the eligible participants both baseline and endpoint mental stress echocardiograms for the same participants. Instead, she only re-read a randomized sample of individuals with baseline results and a different randomized sample of individuals with endpoint results. Despite Dr. Douglas' failure to re-read consistently both of baseline and endpoint echocardiograms for a randomized group of participants who had both baseline and endpoint echocardiograms, she provided a statistical analysis to support her conclusions in paragraph 9 regarding percentages of "agreement" with the original REMIT study findings concerning both baseline and endpoint assessments. Dr. Jiang noted her concern about this weakness in the re-reading evaluation prior to the release of the SCRM report to Donna Kessler on October 16, 2019, in an email. Nonetheless, despite questions raised about the validity of the re-reading of the echo-cardiograms, the SCRM report repeated the questionable conclusions and no action was taken to evaluate Dr. Jiang's concerns with them.

The inconsistencies and missing documentation were previously noted as a result of the original OARC investigation and provided no new information. And despite Dr. Rynn's best efforts to further smear Dr. Jiang's research reputation, again the conclusion was reached that neither Dr. Jiang or any member of the study team falsified or fabricated information in the REMIT study records.

The SCMR committee recommended:

1. The managing editors of the 2012 Am. Heart J. (Jiang et al.) and 2013 JAMA (Jiang et al.) publications should be contacted with the known information about the reporting of the REMIT study conduct and results to determine if corrections and/or retractions may be needed.

2. The Department/CRU, along with Dr. Jiang and the applicable co-authors, should review the other REMIT study publications to determine whether the research is accurately represented in those publications or if the

> managing editors of the journals should be contacted about possible corrections or retractions.
>
> 3. Dr. Jiang should attend a robust workshop on Good Clinical Practice and the requirements of clinical research equivalent to what would be needed to obtain certification as a Certified Principal Investigator or Certified Clinical Research Professional, such as available from the
>
> 4. If Dr. Jiang will be applying for future federal funding to conduct research, she should attend the Responsible Conduct of Research Short Course conducted by the Trent Center for Bioethics or an equivalent program.

After the delivery of the SCRM report and its recommendations, Dr. Jiang took personal leave, and not scholarly leave, as a result of Dr. Rynn's refusal to approve scholarly leave (in an email on August 9, 2019) when she visited China from October 17 to November 22, 2019**.** Dr. Jiang was offered the opportunity to provide a response to the SCMR report by December 6, 2019. On November 12, 2019, Dr. Jiang requested an extension due to her need to carefully consider the report, given that over a year had been spent between the OARC and the SCMR investigations/inquiries, and also due to the fact that while in China, Dr. Jiang was having to care for her 87 year old mother who became critically ill.

On November 13, 2019, Donna Kessler, Duke Research Integrity Officer, replied to Dr. Jiang's request for an extension and denied it, stating that the University's response from the Dean of the School of Medicine Dr. Mary Klotman was due to the US DHHS Office of Research Integrity (ORI) by December 5th. Dr. Kessler did not apparently consider whether the University could or should request an extension of time due to Dr. Jiang's need to spend time taking care of her ill mother. Kessler then reiterated Dr. Jiang's deadline of November 18 to get her comments to Dr. Klotman.

On November 15, Dr. Jiang then reiterated an earlier question that she had made regarding the Echo re-read matter previously raised and included in the SCRM report and again questioned the source of the allegations made to the NIH RIO. On the same day, Kessler replied but did not identify the source of the allegations made to the NIH RIO. With regard to Dr. Jiang's earlier question regarding why only one echocardiogram was re-read for each participant and how the re-read was used to evaluate the REMIT study, Kessler stated:

> The 9.12.2019 Final Report describes the echo review/re-read project to include a randomized samples of images from the REMIT trial representing images from 25/112 of the participants for whom both a baseline and endpoint image was available. The purpose of the review

> was to ascertain the degree of agreement (of MSIMI determinations) in the randomized sample between the re-reads and the determinations presented in the primary paper.
>
> The findings of the 9.12.2019 Final Report are reflected on page 7 of the 10.21.2019 Inquiry Report (item 9), which noted the % agreement in the re-reads, along with a qualitative comment that on average, values obtained for WMSI were lower in the re-reads.

Although not stated by Dr. Kessler specifically in her email, the SCMR re-reads which were conducted by Pam Douglas, M.D. indicated a 79.2% agreement with the baseline MSIMI assessments and an 87.5% agreement with the endpoint MSIMI assessments and noted only that components of the MSIMI scores were lower on average. Again, as noted above, Dr. Jiang had significant concerns about the method used to re-read the echocardiograms and whether the statistical conclusions were accurate. Dr. Jiang had still not been given permission to share the analysis with her caridiology co-investigators.[14]

On November 22, 2019, Dean of the School of Medicine Mary E. Klotman, M.D. authored a communication sent to Donna Kessler, Duke RIO, and copied to Dr. Geeta Swamy, Associate Vice President for Research and Vice Dean for Scientific Integrity. In that communication, Dean Klotman agreed with the SCMR conclusion that confirmed insufficient evidence of research misconduct and agree with the additional corrective actions recommended by the SCMR. Dean Klotman also indicated that she would consider Dr. Jiang's response to the report to be provided by December 5, 2019.

On November 26, Dr. Jiang conferred with the Duke IRB chair Paul Lantos and also with Ombudsman Thomas Metzloff regarding Dr. Jiang's desire to consult with the original REMIT cardiology co-investigators / collaborators who provided the original cardiology and statistical analysis for the original study due to their expertise in echocardiography. Dr. Lantos emailed her and indicated that he "wanted to confirm, having spoken with Jody, that the IRB would like the cardiologists who were on your study to have the opportunity to review and respond to the echo audit, even if they are no longer at Duke." Dr. Jiang had explained that Dr. Rynn had previously instructed her NOT to reach out to the original team who worked on the study because they were no longer at Duke.

In fact, in an earlier email, Lantos had stated the IRB's position more fully:

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[14] In an email in January 2019, Dr. Rynn had forbidden Dr. Jiang to consult with anyone outside of Duke regarding the REMIT study. In fact, Dr. Rynn demanded all the REMIT audit information be kept only among herself, Dr. Scott Compton, Dr. Steve Boyle, Ms. Alifia Hasan, and Dr. Jiang.

> My personal point of view is you did your science as a team and it should be the team that responds to an audit or investigation, especially for something like echo interpretation or statistics for which you have coinvestigators who are experts.
>
> I do not think we as the IRB have any authority to tell you whom you can or can't consult with, nor do we have the authority to override instructions from others to NOT speak with anyone.
>
> Tom will be able to answer this better than I, but I'm not sure you can really be prohibited from speaking with someone unless it's on the advice of Duke counsel or it's a case of protected information that can't be shared. It's worth contesting any instructions you've gotten to not speak with your collaborators if you feel they are unfair or against policy.

On the same date, November 26, Dr. Jiang notified Kessler, the Duke RIO, and Dr. Swamy, the Vice-Dean for Scientific Integrity, that she was reaching out to her cardiology collaborators at the direction of the IRB committee and offered that the process might take longer than the December 6, 2019 date that Dean Klotman had indicated would apply to a response by Dr. Jiang. Dr. Jiang offered to send a brief response without the detail hoped to be provided at a later date by the REMIT cardiology co-investigators.

On December 3, 2019, Dr. Jiang reached out to Dr. Maragatha ("Maggie") Kuchibhatla, the primary statistician of REMIT, and Dr. Steve Boyle, the Lab manager and statistician for Jiang's research on the original REMIT study for via email and provided them with the report from the DCRI Statistic group which explained their conduct of "statistical analysis on the REMIT primary endpoint that was published in JAMA [in] 2013." The report explained that because 20% of the REMIT participants either "did not withhold beta blocker during MS testing and/or did not engage exercise stress testing," the DCRI "requested model re-fitting" without the inclusion of those participants. Dr. Jiang asked Kuchibhatla and Boyle to review and provide her with comments.

On December 12, Boyle responded and indicated that that the attempts to replicate the findings were "mostly successful and the differences were not that problematic." On December 13, Kuchibhatla responded similarly indicating that she was glad that the new results were "not too different from the JAMA results" reported from the primary REMIT study.

Moreover, on that same date, the Duke IRB was provided a copy of the OARC report and reviewed the same on December 19, 2019, to determine whether the event represented an Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO). Having concluded it did not, on December 26, the Duke IRB issued a notice of review stated that no UPIRTSO had occurred and that further the "PI and Investigators, with the support of the CRU and School of Medicine, should seek independent expert opinion on these issues and report back to the Board with their conclusions."

Again, not content with all of her previous discrimination and harassment against Dr. Jiang, Dr. Rynn delivered the crowning blow to Dr. Jiang on January 29, 2020. Dr. Rynn's letter went beyond the scope of all of the previous inquiries / investigations and concluded that Dr. Jiang had engaged in "significant noncompliance with good clinical practice (GCP), FDA regulatory requirements, and institutional policies and procedures" and then took two additional measures, effectively ending Dr. Jiang's research career:

> Effective immediately, per the Chair, Dr. Moira Rynn, Dr. Jiang is no longer approved to propose, submit, or participate in new research related effort as a faculty member of the Department of Psychiatry and Behavioral Sciences at Duke University.
>
> All effort on existing research as Principal Investigator or any other research related effort across Duke Health must end as of June 30, 2020.

In the meeting at which Dr. Rynn delivered her prohibitions to Dr. Jiang, she also informed Dr. Jiang that she, Dr. Rynn, had been the driving force behind the REMIT audits and investigations and admitted that she never actually believed there was a research misconduct.[15]

Dr. Jiang then informed Dr. Rynn that she had a research support fund of $48,847.00 with the Behavioral Medicine Research Center (BMRC). Dr. Rynn then informed Dr. Jiang that she could not use that money for her salary support. Although the BMRC had previously been led by Dr. Redford Williams, Dr. Jiang was aware that Dr. Rynn had removed Dr. Williams from the directorship sometime in middle of 2019 and had herself has been serving the interim director of the BMRC since doing so. Furthermore, Dr. Jiang had a $20,805.40 fund for mental health outreach in her own

[15] Again, note that her instigation of the audits of the REMIT study is not protected under Duke's Non-retaliation and Non-retribution policy because she had no legitimate concern about Dr. Jiang's conduct of the study; she was rather intent on destroying Dr. Jiang's research career and maligning her professional reputation from the outset.

discretionary account, but since March 2019, Dr. Rynn had forbidden Dr. Jiang to leave the Duke campus for any academic activities.

By April 13, 2020, Dr. Jiang had taken several of the required ethics and training course recommended by the SCRM. At that time, Dr. Jiang appealed to Dr. Klotman, the Dean of the School of Medicine, to provide Dr. Jiang relief from the draconian discriminatory and retaliatory measures put in place by Dr. Rynn. She wrote Dr. Klotman, informed her of the same, and also informed her that Dr. Jiang had received a "positive review from the audit of [the] NIMH funded OCEAN trial, a multi-center clinical trial, conducted between 2013 and 2016." Dr. Jiang also informed Dr. Klotman that Dr. Jiang was working on obtaining formal certification as a clinical investigator. Dr. Jiang indicated that she believed that her accomplishments since the audit was initiated by Dr. Rynn in April of 2018 were examples of her "commitment and adherence to the highest standards of clinical research." Finally, Dr. Jiang indicated that Dr. Rynn's actions not only were more restrictive than those recommended by the SCMR and adopted by Dr. Klotman but they also had the effect of ending Dr. Jiang's research career.

Six weeks later, Dr. Klotman responded to Dr. Jiang indicating that she supported Dr. Rynn's actions, which had essentially ended Dr. Jiang's research career. She indicated that the "corrective actions" outlined in the Dr. Klotman's November 22, 2019 letter adopting the SCMR recommendations did not "take into account other audits, reviews, or information known to the Department at the time Dr. Rynn made her decision." Dr. Klotman did not provide any specifics regarding what other "audits, reviews or information" were considered by Dr. Rynn. In fact, Dr. Jiang has never been provided any additional information regarding any additional "audits, reviews, or information" known to Dr. Rynn which would justify essentially ending Dr. Jiang's research career.

When I began this letter to you, I had hoped to be able to limit it to objecting to Dean Klotman's refusal to reverse Dr. Rynn's adverse actions towards Dr. Jiang, but since that time, Dr. Rynn has continued her campaign of unwarranted harassment of Dr. Jiang. Exhibit C summarizes a series of recent emails regarding the desire of Dr. Rynn, through Scott Compton, Ph.D., and Jeannie Beckham, Ph.D., Division Chief, Behavioral Medicine to continue her attempt to use the flawed audit conclusions regarding the REMIT study to further damage Dr. Jiang's reputation among her peers and the public. Dr. Jiang has resisted and will continue to resist reporting the findings of the echo-cardiogram re-reads to JAMA or anyone else until the echo-cardiograms have been re-read by a completely independent group of cardiologists using the same technology and methodology and having the same training as the original cardiologists who generated the data reported in the JAMA publications.

Let me apologize for this lengthy recitation of the facts as they relate to Dr. Jiang. Nonetheless, I hope it is clear to you that Dr. Jiang has been treated in, at best, an unacceptably biased manner by both her department chair, which treatment was subsequently ratified by the Dean of the School of Medicine. At worst, the above recitation of events shows that Dr. Jiang has also been treated differently due to her national origin, gender, and perhaps even her age, by Duke and that she was retaliated against when she resisted Dr. Rynn's efforts to marginalize her, by Dr. Rynn when she took numerous subsequent multiple adverse actions against Dr. Jiang as continuing violations of Dr. Jiang's civil rights since 2018, and then effectively end her research career, all affirmed by the University in Dean Klotman's decision of May 29, 2020.

Dr. Jiang, however, would like to resolve the matters between herself and Duke without resort to litigation. Given however the timeframe, she must be able to do this no later than the end of the month in order to be able to timely pursue these matters fully should Duke decide not to engage in voluntary remediation of the treatment suffered by Dr. Jiang.

I look forward to hearing from you with regard to the University and the Health Systems intentions to remedy the treatment of Dr. Jiang no later than the close of business on November 16, 2020.

With kind regards, I am

Sincerely,

Valerie L. Bateman

VALERIE BATEMAN

cc: Mark D. Gustafson via Email: mark.gustafson@duke.edu
General Counsel
Duke University Health Affairs
Duke University Health System

Robert E. Levin via Email: rlevin@hdmllp.com
Haywood, Denny & Miller, LLP

Att. Exhibit A
Exhibit B
Exhibit C

EXHIBIT A

REMIT Study Inclusion/Exclusion for Initial Consent (Blue color)

Inclusion/Exclusion for REMIT Primary Goal, i.e. Mental Stress Induced Myocardial Ischemia(MSIMI) & Trial Intervention (Red color)

- Patients who exhibited MSIMI during baseline screening were qualified for the trial intervention

Inclusion Criteria

- ❑ Age 21 or greater
- ❑ Clinically stable CHD

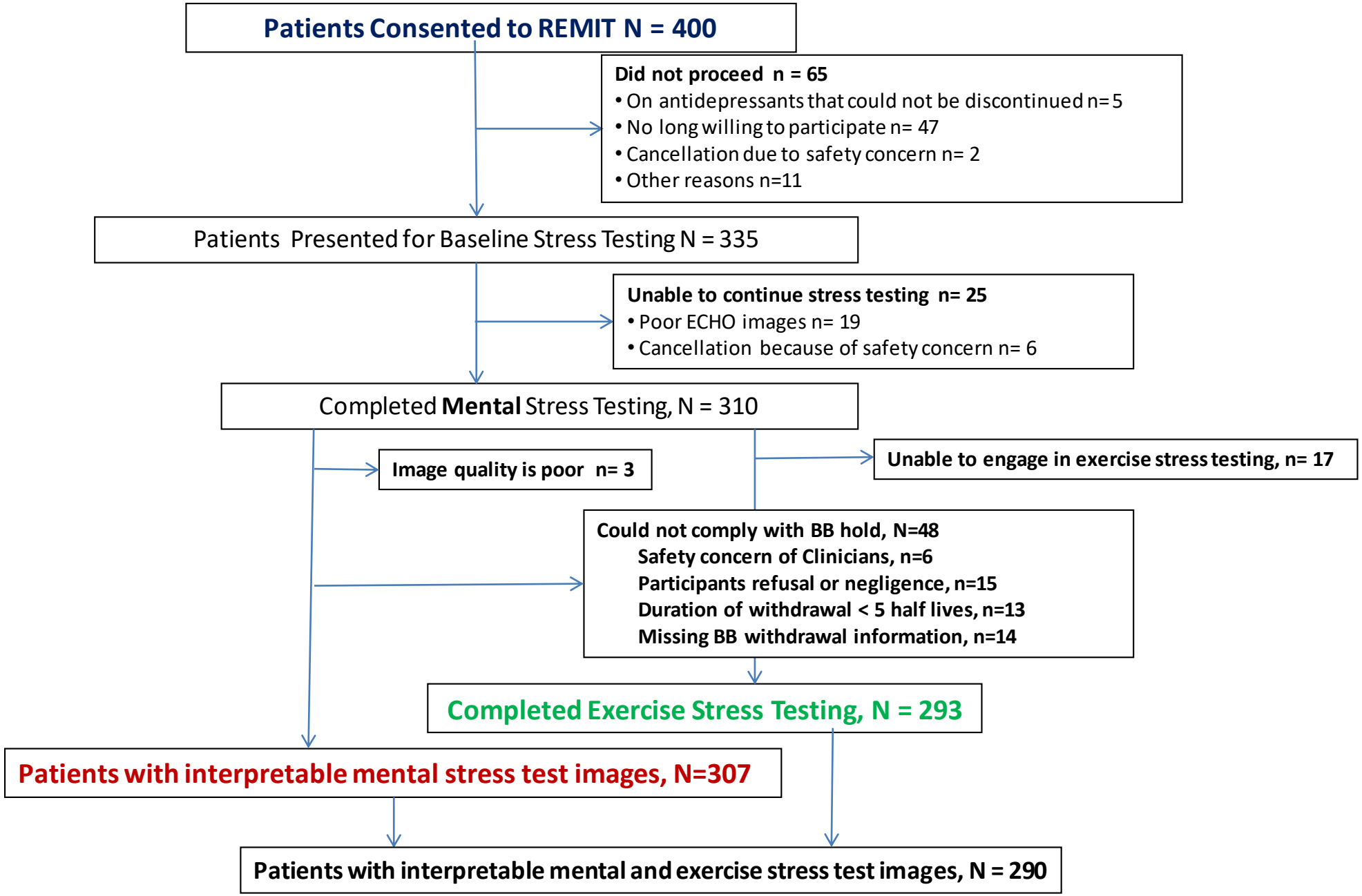
Exclusion Criteria

- ❖ Recent myocardial infarction, coronary artery bypass graft surgery, or other revascularization procedures (≤ 3 months)
- ❖ LVEF < 30% measured by echocardiography, radionuclide ventriculography, or cardiac catheterization
- ❖ Pregnancy
- ❖ Current or previous history of bipolar disorder, cyclothymia, schizophrenia, schizoaffective or schizophreniform disorder, or other psychotic disorders
- ❖ Active suicidal ideation
- ❖ Current substance abuse or history of substance abuse in the previous 6 months
- ❖ Significant cardiac, pulmonary, metabolic, renal, hepatic disease, or malignancy, interfering with subject's participation in this study
- ❖ Seizure (history and/or present) with/without treatment
- ❖ Currently taking antidepressants that cannot be discontinued

Exclusion Criteria

- ❖ Unable to withdraw from anti-anginal medications during ischemic assessment phase
- ❖ Unable to perform exercise testing

Inclusion/Exclusion for REMIT Secondary Goals, e.g. Exercise Stress Test Related Endpoints (Green color)



Consort of the REMIT Study Enrollment & Stress Testing

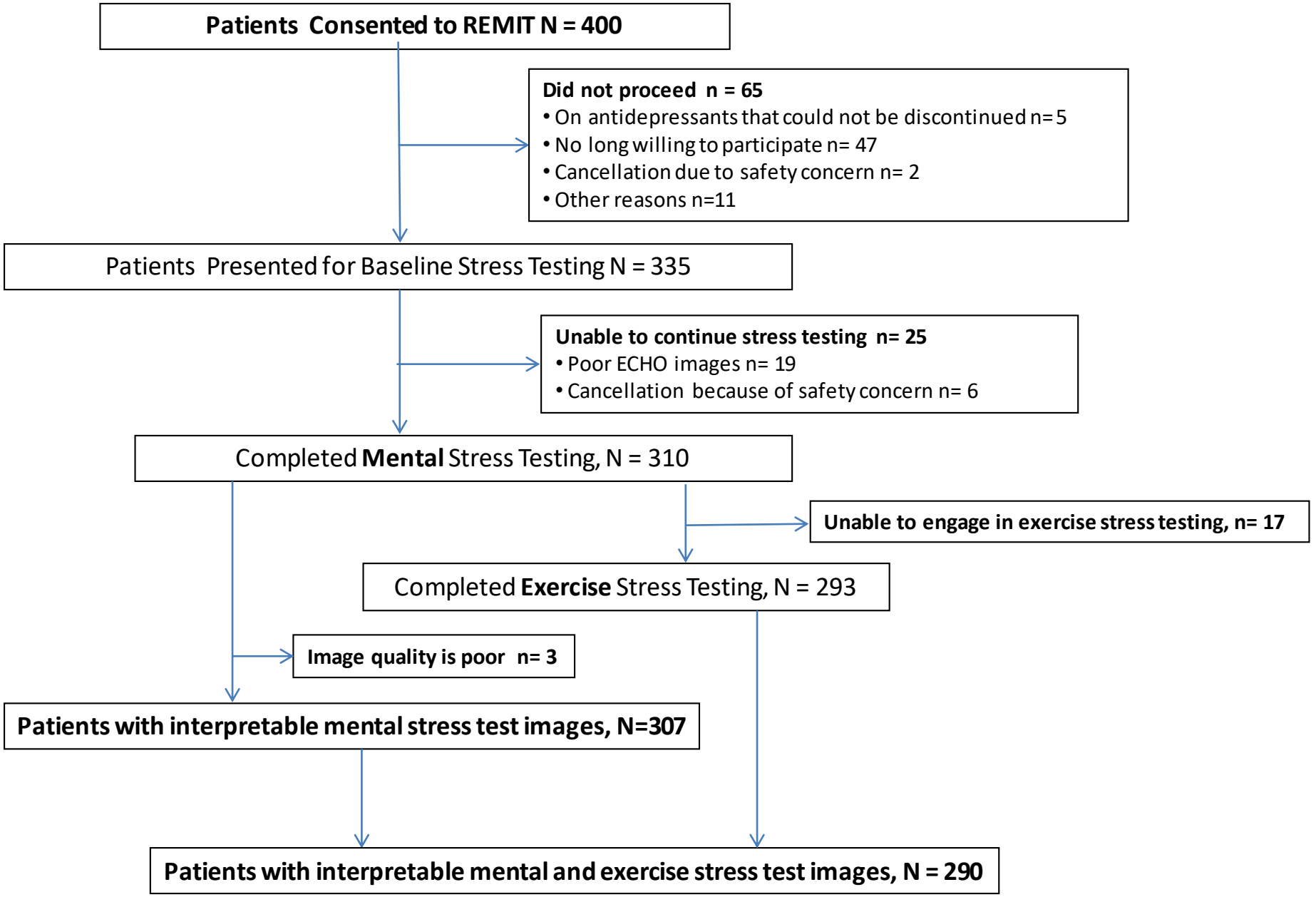


Figure 1. Consort of the REMIT Study Enrollment & Stress Testing

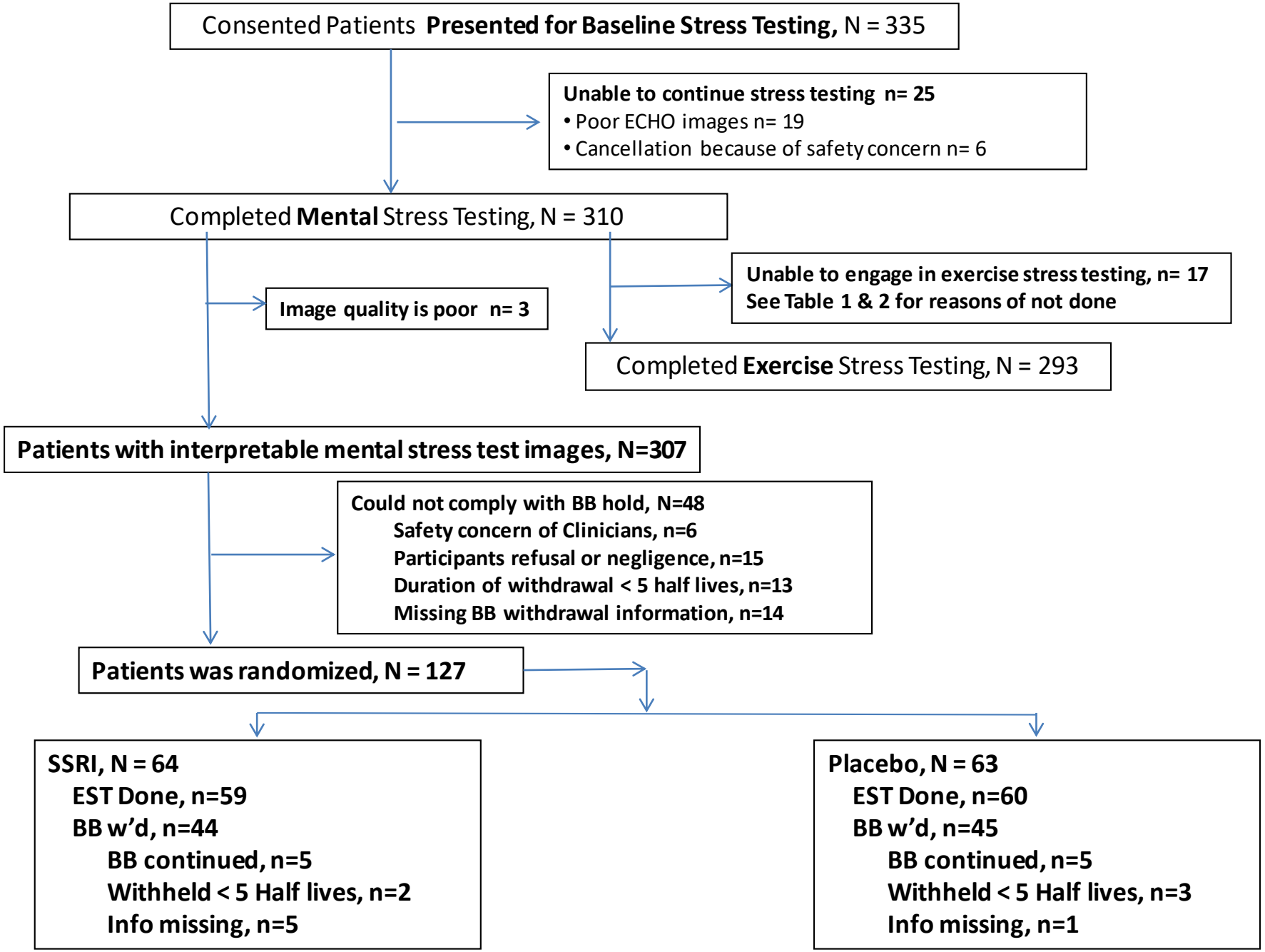
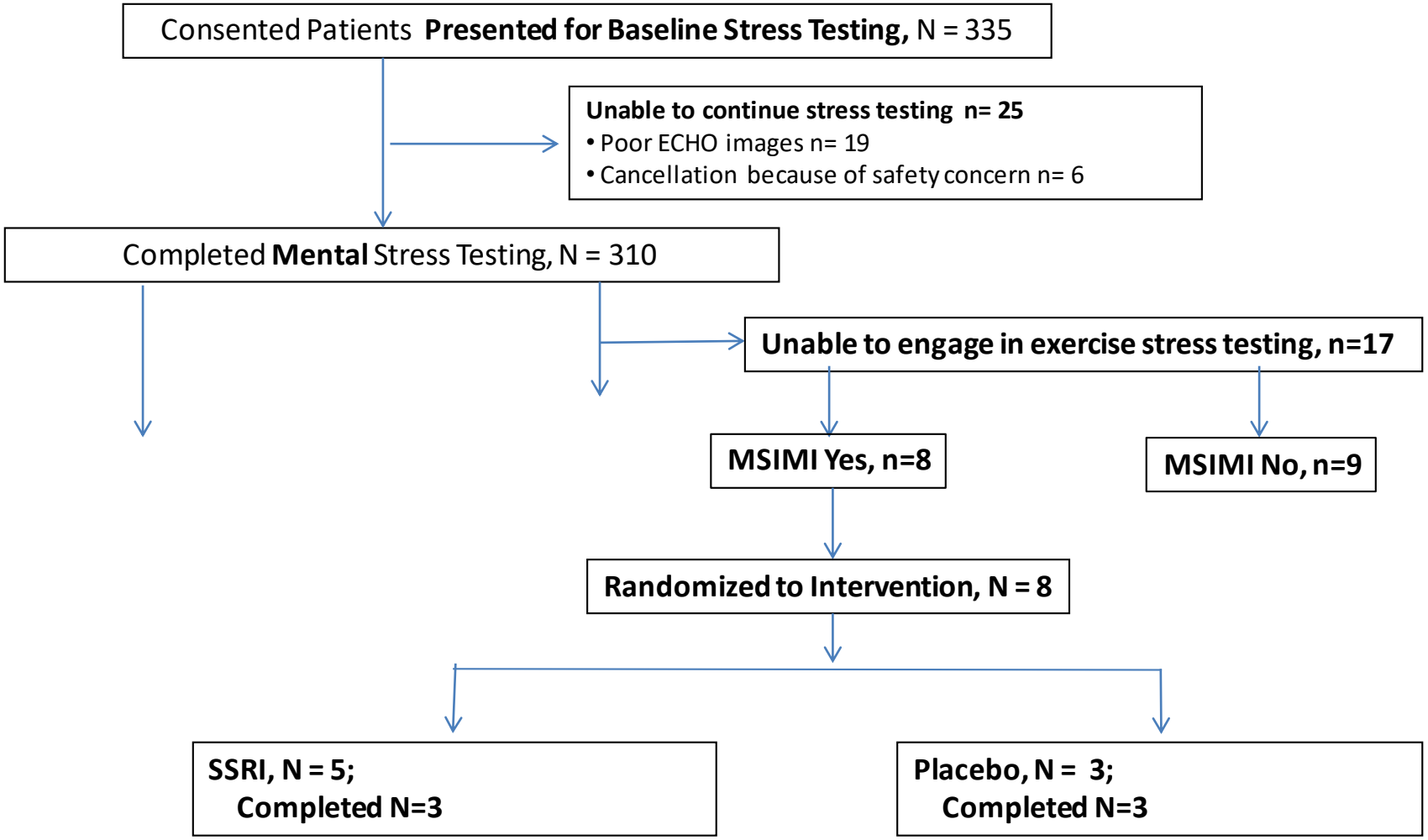


Figure 2. Consort of the REMIT Study Enrollment & Stress Testing with EST and BB Withhold



Categorical Reasons of Participants not Able to Comply EST

CV safety concern by Clinicians	N=4
Lab Technique concern – WT too high	N=1
Pain in extremities	N=5
PT preferred not to have it done due to fatigue	N=6
Schedule conflict	N=1

Figure 3. Consort of EST Non-compliance in the REMIT Study Enrollment & Stress Testing

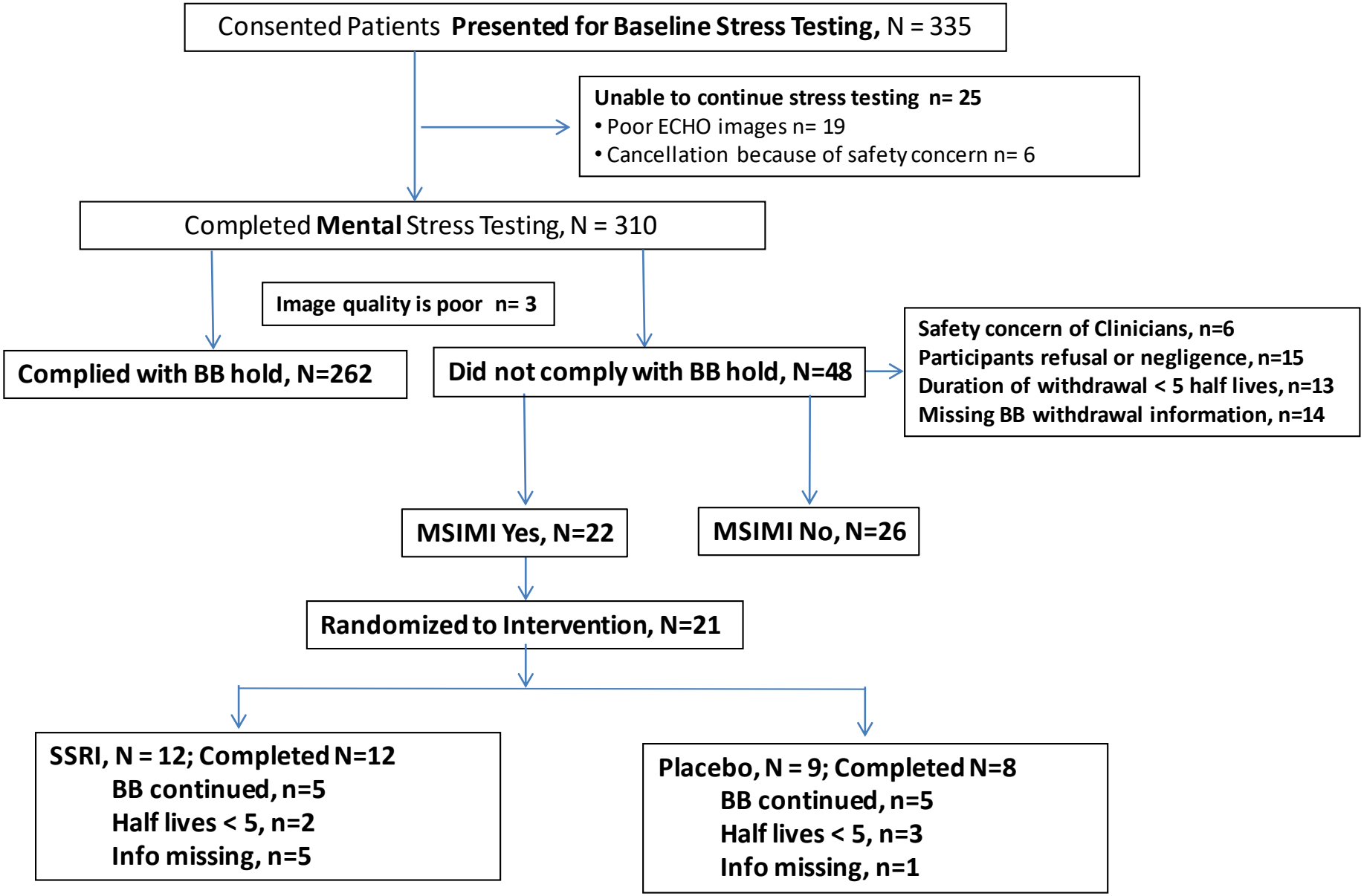


Figure 4. Consort of BB Non-compliance in the REMIT Study Enrollment & Stress Testing

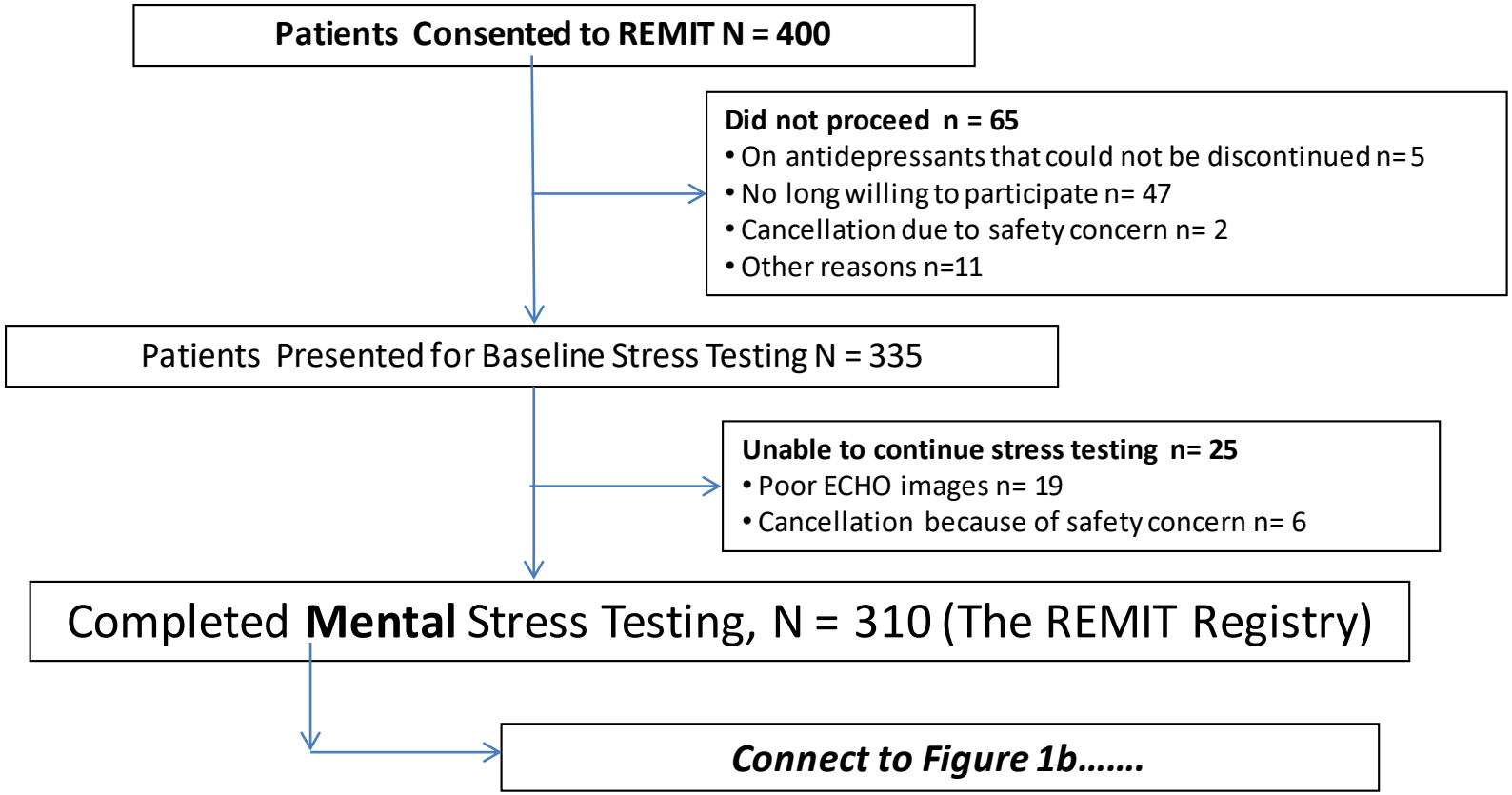


Figure 2a. Consort of the REMIT Study Enrollment & Stress Testing

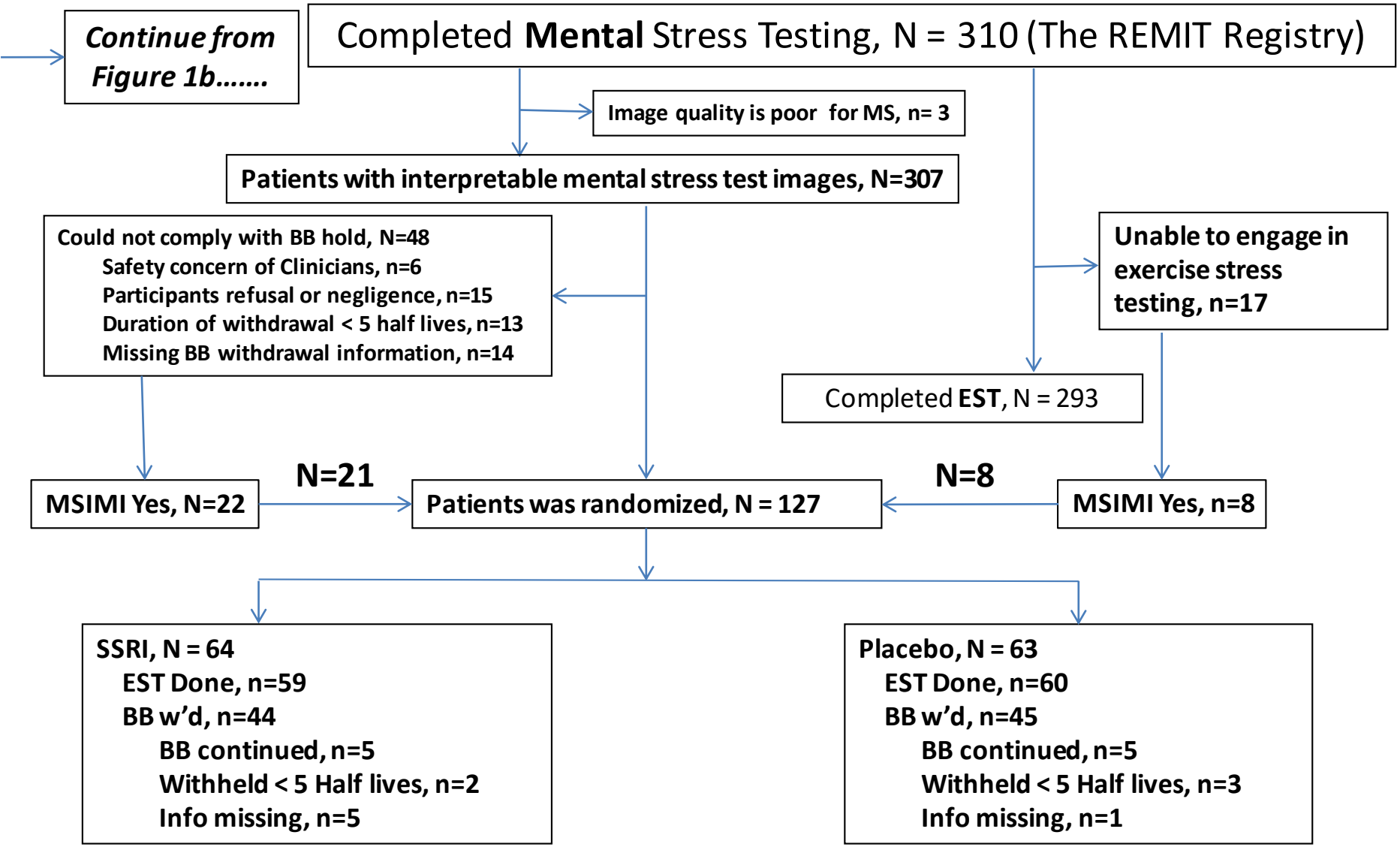


Figure 2b. Consort of the REMIT Study Enrollment & Stress Testing with EST and BB Withhold

EXHIBIT B

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
Patient Eligibility			
1. 26 of 127 REMIT study participants randomized to the study intervention were not eligible for the study (either for entrance into the study or randomization / continuation), in accordance with the inclusion/exclusion criteria specified in the protocol.	1. Observation: Eligibility: 4 of the 25 subjects reviewed were determined to be ineligible. (p4)	**1st Audit:** Page 4, 5th bullet: It was documented that subject 005 was not able to come off beta blockers for 72 hours. The subject was able to come off the beta blockers for 24 hours. Per the protocol subjects that are unable to withdraw from anti-anginal medications during ischemic assessment phase should be excluded from the study. Per the protocol, the entire process of cardiac medication withdrawal will be monitored by the study PI and cardiology investigators. There was no documentation that indicated that monitoring of cardiac	It is not accurate to state that these participants were "not eligible" for the study because the original protocol changed in response to patient safety concerns. They were clearly eligible under the protocol used, again as amended to ensure patient safety. It was necessary to modify the protocol to not withhold Beta blockers prior to the stress testing, and/or not to engage in exercise test, due to a need to ensure the safety of these participants in the study. This modification in the protocol did not affect the primary goals of the study and all changes in protocol were transparent to the JAMA publishers and readers.

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
		medication withdrawals occurred. **2nd Audit:** Page 2. From a total sample size of 127, 26 (or 20.5%) of the randomized patients did not meet one or more eligibility criteria.	In 2012, it became clear that it was the PI's primary responsibility to notify IRB of such modifications in protocol. During the years of 2006 to 2011, the time period of the REMIT study, there was no such requirement for PIs and the primary responsibility of the PI was to ensure the safety of study participants, which the change in protocol was intended to do. Even under the current policy, approval of the IRB is not required prior to making changes to the protocol to protect patient safety. *The first Duke IRB protocol amendment requirement made by Jiang and her research team was dated in May 2011. * Duke IRB responded to the CRU 2nd Audit and Jiang's response to the audit as the following: "The purpose of this e-mail is to notify you

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			that IRB review of the following safety event is complete and the IRB has declared that the problem/event does not represent an Unanticipated Problem Involving Risk to Subjects or Others (UPIRTSO). No further action is required."
Further, the documentation in the study records regarding missed assessments and the rationale for waivers (by the study team) of inclusion/exclusion criteria was incomplete.	Page 4-5: Poor documentation practices were observed throughout the trial making it difficult to assess the accuracy of data transposed from the original source. **o** For many subjects, data was generated during treatment, but recorded on forms version-dated after subjects completed treatment. It is unclear if data was transcribed from earlier form versions not found in subject files or where	Page 3-4: There were several instances observed where source document worksheets were not fully completed. Documentation of who completed source worksheets was not consistently documented. Also, headers were not consistently entered on the worksheets. **o** There were instances where visit worksheets were missing. It was not clear if the worksheets were not filed or if the	The main reasons underlying these issues were due, and/or related, to the followings: 1. There had been some **rapid turnover of research staff** members in Jiang's laboratory who worked on REMIT. The rapid turn rate was due that majority of the research staff members were young who were in progress of moving upward in education / academic career. In the context of intensity recruitment and testing of the study, some of the staff missed collecting data and including it in the clinical

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
	original data was housed in the interim months or years. **o** Paper data did not consistently match the electronic Access database. The PI and statistician confirmed the database was used for publication. It is unclear if changes were made directly in the database or how corrections on paper forms were read by the Access scanner. o Multiple sets of forms were used throughout the trial with no audit trail to explain when newer versions should be used. o Forms were not designed to capture dates data was recorded or by whom. o Corrections were not lined out, initialed, explained or, in some cases, substantiated by source. The percentages	visit did not occur. If the visits did not occur there was no documentation to indicate these occurrences. **o** There were a number of instances PHI on subject files (i.e. medical records) were not properly redacted. PHI located on medical records should be redacted to ensure the privacy of the subjects are maintained. Per the protocol, subject names and identifying numbers will be kept on separate forms in a locked office separated from data files, and only the study coordinator and study physicians will have access to subject identities. □ There were source documents in each subject folder that were not filed according to the appropriate study visit. Some documents were	research file (CRF), and then passing it on to the next person. But the next person might have not had time to catch up. The lab did in fact have a plan to get all data existing in several different places into the consolidated CRF. 2. In addition, during the study, the lab was required to transition from paper data collection to electronic data collection and entry. Some staff members liked to scan the paper data, and once they did so, the staff did not always return the paper data to the appropriate CRF. 3. All echocardiography images, wall motion scores and LVEF scores are stored in the Duke Echocardiography Laboratory Database (DELD). The DELD maintains a comprehensive digital archive of all clinically performed echocardiograms linked to a searchable reporting database. Our

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
	of coronary artery stenosis on baseline forms were changed for 52% of subjects reviewed, and forms either missed sources to justify the changes and/or contradicted sources in subject files.	filed in an unorganized manner. It was difficult to determine where these worksheets needed to be filed.	collaborators, Eric Velazquez, MD and Zainab Samad, MD provided us with an electronic version of the wall motion and left ventricular ejection fraction scores, which are stored on a shared drive (S:\Sadhart\REMIT\REMIT Database\EF and Wall Motion). Because all data on paper were being transferred to electronic database, there was no need to keep the Echo data on paper. 4. Another factor which affected the data compilation and organization was the result of Dr. Jiang's lab being forced to move to another location by Edward C Suarez Ph.D., after he became the Department CRU director sometime between 2011 and 2012. Jennifer Wilson was the research coordinator, and the only staff member in Dr. Jiang's lab able to take care of move. Because the move was also very sudden and required to occur over a very

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			short period of time, Jennifer Wilson had no time to organize the REMIT study materials as she wished. The move significantly affected the organization of the REMIT study records significantly and was beyond the control of either Dr. Jiang or the research staff. 5. In addition, Dr. Jiang's lab started another multi-center clinical trial soon after the lab was moved to the new location. Jennifer Wilson was required to expend significant effort on the new trial and was not able to prioritize the re-organization of the data for the REMIT study, and combined with the significant personnel changes in the clinical research team, resulted in the delay in organization. 6. After the multi-center trial was closing up, Jennifer Wilson started organizing REMIT study materials. Unfortunately, she then got a job offer from Duke

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			Cardiology division that was too good to decline. She passed the duties to Pamela Bonner who was hired by us to take over from Jennifer. Again, Pamela Bonner was unable to complete the reorganization of the materials prior to her departure from Dr. Jiang's lab, which was Dr. Rynn led Dr. Jiang to believe was the result of her objections to lab practices, which Pamela Bonner later denied making. All of the missing data issues have been addressed and corrected.
There were also inconsistencies identified across the paper and electronic records for the study.	Page 4-5: **o** For many subjects, data was generated during treatment, but recorded on forms version-dated after subjects completed treatment. It is unclear if data was transcribed from earlier form		Please see above responses.

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
	versions not found in subject files or where original data was housed in the interim months or years. o Paper data did not consistently match the electronic Access database. The PI and statistician confirmed the database was used for publication. It is unclear if changes were made directly in the database or how corrections on paper forms were read by the Access scanner.		
This was determined by the Departmental Clinical Research Unit (CRU) in reviewing study and medical records for each participant.		*Please see the 2nd Psychiatry department Audit report and Dr. Jiang's response to the 2nd department audit.	The Duke IRB responded to the Audit and Jiang's response to the audit as the following: "The purpose of this e-mail is to notify you that IRB review of the following safety event is complete and the IRB has declared that the problem/event does not represent an Unanticipated

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			Problem Involving Risk to Subjects or Others (UPIRTSO). No further action is required."
2. Most ineligible participants either did not/could not hold their beta-blocker medication before the stress tests (i.e., did not stop taking their usual dose of the beta blockers) or were unable to perform the exercise stress tests.	Page 4: 16% of subjects reviewed were ineligible per protocol inclusion/exclusion criteria. • 44% of subjects reviewed were missing documentation required to confirm eligibility. • 24% of subjects reviewed, all toward the end of the study, were screened using additional "safety criteria" that were stricter than protocol-approved criteria. These criteria were never used to screen subjects enrolled through the first three years nor were they ever formally incorporated into the protocol. It is unclear if	Reported in the 2nd Department Audit (Page 2-4), 13 REMIT participants were not able to withhold Beta-blockers prior to baseline stress testing, and 8 could not perform exercise tests. Of these participants, 2 of them were not able to do neither.	It is not accurate to consider such protocol amendments as "violation of eligible inclusion /exclusion criteria." All those participants were considered able to do both during recruitment screening and when they provided the study consent. Something might have changed during the waiting period prior to the patient coming to the lab for the stress testing. The primary concern of the clinical trial was to ensure the safety of these participants and the need to not alter the primary study endpoint. Thus, the protocol for inclusion/exclusion was amended; amendments of protocol are common when safety issues arise and the amendments have no or little

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
	subjects enrolled in the first portion of the trial were at greater risk because they were not screened or enrolled using this "safety criteria."		impact on the actual study hypothesis.
3. Dr. Jiang provided verbal testimony that the primary goal of the study was to evaluate the effects of escitalopram (an SSRI) versus placebo on mental stress induced myocardial ischemia (MSIMI) and participants were viewed as "eligible" for randomization if they tested positive for MSIMI during the baseline testing.			Having REMIT participants withholding Beta blocker prior to stress testing was originally included for a secondary purpose of the study. Beta-blockers reduced the heart rate which masked the true response of exercise stress testing. The PI and co-investigators were originally hoping to collect data to be able to enhance their understanding of the differences of mental stress-induced ischemia vs. exercise induced ischemia but were not able to do so for some of the participants.
4. In Dr. Jiang's view, completion of exercise			This was not only Dr. Jiang's view, this was the view held

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
testing was not the primary interest of the study.			by all of the co-investigators. While much ado has been made of the fact that some participants in the study were not required to complete exercise testing or withhold beta blockers, neither of these affected the team's analysis of the data collected during the study. Had Dr. Jiang been permitted to consult with her collaborators who were external to Duke from the beginning, this point could have been made early on and perhaps saved a great deal of time and resources expended by Dr. Rynn in an attempt to sabotage Dr. Jiang's research career.
Dr. Jiang explained in her testimony, if participants were unable to complete exercise stress testing at study visits (such as for safety reasons), they were still randomized and/or			Yes. This is because if participants were suffering from mental stress induced myocardial ischemia (MSIMI) during baseline assessment, they were eligible to participate in the

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
allowed to continue in the study.			study and take the study drug. Please see above for additional details regarding the lack of import of the exercise stress testing and withholding of beta blockers.
Participants were also not asked to come back to the clinic to perform exercise tests because the mental stress testing (to evaluate MSIMI) was the primary goal of the study.			Since exercise test was not the primary goal of REMIT study, as explained above, it was very difficult for a participant to return for the exercise test and they were not required to do so. This was in fact a patient safety issues as well due to the difficulty of the return visit for the patient.
5. Mental stress testing was performed during the study whether or not the participants held their beta blocker medications, as recorded in the study records.			Dr. Jiang and her collaborators knew that beta blockers have no effects on mental stress induced myocardial ischemia; thus, it was not necessary for beta blockers to be withheld for the primary purpose of the study to be accomplished.

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
Dr. Jiang explained in her testimony the primary reason for holding beta blockers was for the exercise testing. She also stated, "we already know" beta blockers do not affect mental stress testing.			
6. As confirmed in verbal testimony from both Dr. Jiang and Ms. Wilson, Dr. Jiang, was responsible for confirming subject eligibility prior to randomization.			Dr. Jiang verified the testing results and eligibility prior to randomization. All 307 participants were eligible for inclusion in the study and were included. The continued repetition of the statement that "ineligible" patients participated in the study does not make that conclusion any more valid. **Only eligible participants were included.** Eligibility was determined by the existence of MSIMI, without regard to exercise stress testing or the taking of beta blockers.

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			Put simply, patients who demonstrated mental stress induced myocardial ischemia (MSIMI) during the REMIT baseline assessment would be qualified for randomization to study medication / placebo.
7. No amendments were submitted to the IRB regarding changes to the inclusion/exclusion criteria during the study, nor were any requests submitted to the IRB to waive inclusion/exclusion criteria for one or more subjects, as confirmed in IRB study records.			Arguably, it was unnecessary for the REMIT protocol to be amended for the modification eliminating the requirement that Beta-blocker usage be discontinued and the participants undergo exercise testing because the elimination of those requirements **reduced** risk to the participants, not **increased** it. Moreover, because those requirement were not necessary to the primary study endpoint; they were only for possible secondary purposes of the study. If the PI or the co-investigators had known or believed it to be critical for the IRB to be notified of the

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			amended protocol which reduced the risks to the participants, not increased it, prior to doing so, certainly they would have taken additional steps to ensure that the IRB was notified. But the fact that the beta blockers were not discontinued and that exercise stress testing was not required again **reduced the risk to the participants** and had **no effect on the study's primary focus.**
8. The presence or absence of MSIMI was not determined by Dr. Jiang, but by members of the cardiology study team as confirmed in testimony from Drs. Jiang and Boyle.			Dr. Jiang is not a cardiologist; necessarily and per the protocol, whether or not a REMIT participant developed myocardial ischemia was determined by the study cardiologists.
9. Re-reads of echocardiograms used to evaluate MSIMI by			Dr. Jiang does not consider Dr. Pam Douglas to be an independent cardiologist for

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
independent cardiologists (Appendix J) showed a 79.2% agreement with baseline MSIMI assessments and 87.5% agreement with endpoint MSIMI assessments. However, the percent agreement of Ejection Fraction/EF (one of two components of MSIMI) was lower with 40.9% agreement at baseline and 70.8% at endpoint. Values for Wall Motion Score Index/WMSI (the second component of MSIMI) were, on average, lower in the re-reads than in the original published findings.			the REMIT echo re-reading since she has been working at Duke for many years. She was in fact very familiar with the two original echo-cardiologists and may in fact have had personal dealings with them. She was also well informed of the purpose of the REMIT study. Furthermore, analysis of an Echo image is a very subjective process requiring training and collaboration. An echo-cardiologist who plan to analyze the mental stress induced ventricular motion change needs particular training. The well accepted method in this field of research is to have consensual reading from at least two well trained echo-cardiologists. Dr. Douglas did not comment on who re-read the REMIT echo images, or whether the re-reading was consensual. Nor did Dr. Douglas provide

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			any insight into how the EF values were scored. For REMIT, per protocol, the echo-cardiology lab used software to analyze the REMIT echo images and produce the EF scores. The REMIT cardiologists validated these measurements. Dr. Douglas only re-read a proportion of REMIT echo images. The reason behind her decision to only re-read selective images is not known. Any re-read of Echo images of the heart would yield different scores, even if re-read by the same person. The REMIT cardiologists had themselves trained and tested for REMIT and they did not have 100% agreement when even they, as trained echo-cardiologists, read the images separately.

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
10. A number of errors in the 2013 JAMA publication were identified in the 4.11.2019 statistical re-analysis report (Appendix H), including: a. The number of participants listed in Table 1 as "total with history of diabetes" was actually "total without history of diabetes." b. The "resting heart rate" in Table 2 was actually "weight in kg." c. The standard deviations for "trait anxiety" in Table 2 were incorrect. d. The "resting negative and positive affect" in Table 2 were			Minor errors occur quite often in medical journals. For the papers at issue, those errors were related to multiple revisions during which some forms and/or characters got replaced. The final proof reading was not careful enough as well. Nonetheless, for the minor errors noted, Dr. Jiang is happy to send an errata notice to JAMA.

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
actually "mean negative and positive affects." e. The p-values in Table 3 were labeled as Fischer's exact tests but were actually chi-square tests. f. The data presented in Table 4 has an extra placebo patient. g. The models in Table 5 were not adjusted for age even though the footnote indicates they were. h. The column headers in Table 5 are labeled incorrectly as "odds ratios" but are actually "LS Means."			

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
11. The 9.12.2019 reanalysis report (Appendix J) points out that the REMIT study protocol was ambiguous with respect to the definition of the primary endpoint. It states both that, "the primary efficacy outcome will be the **occurrence of MSIMI** at the end of the 6-week treatment" and "the primary efficacy measure is the **improvement or worsening of MSIMI** at the end of 6-weeks of treatment from baseline assessment." ***These two standards are significantly different, with the second being much stricter.***			The "independent reviewers" were incorrect when they stated that two different standards were applied to the data and that a "more lenient" standard or definition was used in the 2013 publication. In fact, only one standard was ever used: ***the measurement of MSIMI at the end of the 6 weeks of treatment with either the study drug or a placebo.*** The fact that the measurement of the MSIMI at endpoint was described as "the occurrence" in one place and as "the improvement or worsening" in another place does not create more than one standard, either more lenient or stricter: the study compared the baseline measurement of MSIMI to the endpoint measurement of MSIMI for all participants to draw conclusions about the

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
The independent reviewers agree that the more lenient definition appears to be the one used in the 2013 JAMA publication.			efficacy of the drug versus the placebo.
12. Based on the 9.3.2019 report from the independent cardiologists (Appendix I), the study design with respect to collecting and analyzing echocardiograms for MSIMI determinations (which is the central focus of the REMIT study) was **not optimal** and contributed to the difficulty of reproducing the findings.			Dr. Douglas has no expertise in mental stress testing and mental stress induced myocardial ischemia and her 2019 conclusions about the "study design" not being optimal was made without any scientific support or analysis. Nor was this conclusion explained with regard to what was in 2006-2011 "state of the art" research. Mental stress induced myocardial ischemia (MSIMI) in the REMIT study came from two measurements: 1. Wall motions, and 2. EF scores.

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			The wall motion scores, such as better, worse, or same, were generated by the two cardiologists and the EF scores differences were calculated by study statisticians, upon the true values the Echo lab provided the investigators. The study then considered the deviation (depression or elevation) of ST-segment of ECG in 2 or more leads lasting for ≥ 3 consecutive beats, occurring during at least one of the 3 mental stress tasks. The protocol stated: <u>Wall Motion</u> Wall motion of left ventricle will be assessed using the American Society of Echocardiography (ASE) recommended 16-segment model. Motions of each segment will be graded and scored based on either normal (normal or hyperdynamic, score = 0) or

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			abnormal (hypokinetic, akinetic, or dyskinetic; scores = 1, 2, or 3, respectively). WMSI will be calculated at rest and for each mental stress task and exercise test as the sum of the scores divided by the total number of segments scored. This scoring system has been validated by other investigators with coefficients of correlation for intra-observer and inter-observer variability of 0.81 and 0.84, respectively (Gottdiener 1994). <u>LVEF</u> LVEF is calculated based on measuring the images of the three windows (parasternal long axis, apical 4-chamber, and apical long axis) (see figure below for reference). **The primary study endpoint is the**

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			improvement or worsening of MSIMI at the end of 6-weeks of treatment compared to baseline assessment between the escitalopram and the placebo groups. For evaluation of the primary study endpoint, wall motion will be first reviewed and scored SEPARATELY by two experienced echo cardiologists (Dr. Velazquez and Dr. Samad) who will be blinded to the treatment assignment and tasks. The steps of the review and scoring will be carried on as 1. Baseline assessments, 2. end of 6-week intervention, and 3. Side by side comparison as comparing to baseline, is the wall motion during the end of intervention better, no change, or worse. The scores for each test and each subject obtained by the

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			2 cardiologists will then be compared for concordance. For the ones that are not concordant between the two cardiologists, a consensual review/scoring will be applied. Differences of LVEFs obtained from resting and mental stress testing both at end of 6-week intervention will be compared to the LVEFs obtained at the baseline."
13. According to information from the IRB and Department/CRU, Dr. Jiang is relatively inexperienced as a Principal Investigator and the REMIT study is the first PI-initiated, interventional and randomized clinical study for which she has had primary responsibility.			Dr. Jiang is highly experienced with mental stress testing and mental stress induced myocardial ischemia, the study design, the pharmacological intervention, etc. Dr. Jiang was not experienced with administrative issues when the REMIT study began nor did she understand that the staff turnover, the moving of the lab, and the transition

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			from paper to electronic documentation would have such impact on the subsequent review of the study results some eight years after the study concluded in 2011. Dr. Jiang had no way to knowing that IRB and DOCR policies and procedures would undergo significant revisions in the time period after the actual clinical trial was conducted, nor that those standards would be applied to the study which occurred many years earlier. Dr. Christopher O'Connor, and Dr. James Blumenthal would be able to comment on Dr. Jiang's qualifications and abilities as a PI. In addition, Dr. David Krantz and Dr. Ranga Krishnan (outside of Duke) would also be able to comment on Dr. Jiang's qualifications and abilities as a PI.

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
14. Based on testimony from Ms. Wilson and Dr. Jiang, there was a significant amount of staff turn-over on the REMIT study team while the study was being conducted.			The rapid personnel change might had some staff members not able to catch up with the intensive work of REMIT quickly. They might have wanted to catch up with data collection /record documentation, but later forgot or left the lab without having other staff members to catch up. See above.
15. Based on testimony from Dr. Jiang, the funding for the REMIT study from NHLBI was limited and she was not able to obtain additional money from her department for the study. Dr. Jiang indicated she had a significant clinical practice and other research efforts ongoing while the REMIT study was being conducted.			The overhead paid to the department and the school of medicine from the NIH for the Remit study could have been used to fund an individual from the Clinical Research Unit to evaluate the quality of the study. Dr. Jiang in fact asked the department to use such funds to pay for such a monitor but her request was not granted.
16. The 2012 Am. Heart J. publication (Jiang et al.) and 2013 JAMA publication			The 2012 American Heart Journal paper was the REMIT method paper that

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
(Jiang et al.) state, "…all stress tests were conducted…following 24-28 hours withholding of beta-blockers," but this is not accurate.			published the original protocol of the study. See excerpt below. It did not report any results of the study. **METHOD** In this single-center randomized clinical trial, adult patients with clinically stable CHD are recruited for baseline mental and exercise stress testing assessed by echocardiography. In addition, psychometric questionnaires are administered, and blood samples are collected for platelet activity analysis. Patients who demonstrate MSIMI, defined by new abnormal wall motion, ejection fraction reduction ≥8%, and/or development of ischemic ST change in electrocardiogram during mental stress testing, are randomized at a 1:1 ratio to escitalopram or placebo for 6 weeks.

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			Approximately 120 patients with MSIMI are enrolled in the trial. The stress testing, platelet activity assessment, and psychometric questionnaires are repeated at the end of the 6-week intervention. The hypothesis of the study is that SSRI treatment improves MSIMI via mood regulation and modification of platelet activity. **CONCLUSION** The REMIT study examines the effect of SSRI on MSIMI in vulnerable patients with CHD and probes some potential underlying mechanisms. (Am Heart J 2012;163:20-6.) ***Thus, the 2012 paper accurately stated the original protocol which intended to withhold beta blockers prior to baseline testing.***

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			The 2013 JAMA paper reported the results of the REMIT trial which had as its objective "to examine the effects of 6 weeks of escitalopram treatment vs placebo on MSIMI and other psychological stress-related biophysiological and emotional parameters." This article clearly stated that **"[t]he majority of the participants were taking aspirins, statins, and beta-blockers .** . . . No differences in medication use by treatment groups were noted." In addition, the JAMA publication also explained "[p]atients who exhibited MSIMI during baseline screening were qualified for trial intervention." The presence or absence of beta-blockers was not used as an inclusion or exclusion factor. The paper clearly explained the study flow for the REMIT trial and stated that 56 of the

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			original group of 64 who received escitalopram completed the study and 56 of the 64 who received a placebo completed the study. In addition, Table 1 also clearly explained that of the 63 patients taking the escitalopram, 55 of them **were taking beta blockers at baseline** and throughout the six week drug intervention and 54 of the placebo takers were taking a beta blocker at baseline and throughout the six week intervention.. Of these patients who were randomized to the REMIT drug intervention, 5/64 (7.8%) on Escitalopram and 1/63 (1.6%) did not withhold their Beta-blocker for the baseline stress testing. . The rest of the drug intervention participants (95.3%) withheld their Beta=blocker for the baseline stress tests (Appendix A Figure 2.).

SCRM FINDING	OARC FINDINGS	CRU FINDINGS	RESPONSE
			The REMIT team published the detailed Beta-blocker withholding for baseline stress testing data in their REMIT baseline data analysis paper in JACC 2013. ***Thus, SCRM finding that the inclusion of the sentence in the 2013 JAMA publication*** that, "…all stress tests were conducted…following 24-28 hours withholding of beta-blockers" is accurate, but the article itself clearly indicates that the inclusion of the statement about the presence or absence of beta blockers ***had no impact on the conclusions of the study as a scientific matter.***

EXHIBIT C

EMAILS REGARDING COMMUNICATING TO JAMA "ISSUES" WITH REMIT STUDY

From: Wei Jiang, M.D.
Sent: Thursday, November 5, 2020 10:13 AM
To: Scott Compton, Ph.D. <compt004@duke.edu>
Cc: Dr Moira Rynn, M.D. <moira.rynn@duke.edu>
Subject: RE: A Zoom to discuss next steps Re: REMIT

Scott,

I have read the letters you drafted. I regret to inform you that I cannot sign either of those letters because they are inaccurate and misleading. I will be happy to send you my specific objections to the statements in the letters that I find objectionable if you would find that helpful.

With regard to your statement that "[w]e need to move forward with the corrective actions made by the Standing Faculty Committee regarding the REMIT project. Specifically, we need to let the editor of JAMA know about the findings from the internal review and the results from the re-analysis conducted by DCRI on the smaller sample," I will simply say this:

1. On December 19, 2019, the IRB specifically stated in its review the following:

On the question of data integrity, the reviewed data on how many subjects met the specified inclusion/exclusion criteria (which is still under independent review), who did the stress tests, how they were interpreted, who interpreted the ECHOs, the quality of the ECHO, how the data were used on those patients not eligible for protocol (e.g., those who could not be taken off beta blockers), those who did not have stress tests, and whether the published papers truly reflected the way the study was actually done, could not be answered. There are enough questions raised in the internal OARC audit, that the board needs to see expert opinion, independent of the study team, on the interpretation of the stress tests, ECHOs and how the ineligible patients were handled in reporting the data before it can make a determination. The PI and Investigators, with the support of the CRU and School of Medicine, should seek independent expert opinion on these issues and report back to the Board with their conclusions.

2. In fact, someone (not me, as the Principal Investigator, nor my co-investigators as recommended by the IRB) commissioned a review by Dr. Pam Douglas with the DCRI. I do not consider her evaluation either "independent" or "expert" on the subject of the evaluation of the ECHO images, and I raised my objections to Donna Kessler to the method and conclusions of Dr. Douglas in an email prior to the finalization of the 10.22.2019 report. These objections were neither included in the report nor was any action taken as a result of them.

3. The IRB itself indicated that questions about the "data integrity" of the REMIT study could not be answered without additional information. The board indicated that it needed to see "expert opinion" independent of the study team, " on the interpretation of the stress tests, ECHOs and how the ineligible patients were handled in reporting the data before it can make a determination." Unfortunately, that has not occurred and the IRB has never weighed in on the integrity of the data from the REMIT study and its subsequent publication.

4. Thus, in my opinion, the findings of the internal review are, as found by the IRB, "incomplete" and the DCRI evaluation is deeply flawed and should not be reported to JAMA. In fact, I believe that doing so would be professionally and scientifically irresponsible given the IRB's conclusions.

You are **NOT** authorized to submit any correspondence on my behalf to anyone. If you do so, I will inform the recipients as well as the Duke University Office of Legal Counsel of your unauthorized actions.

I appreciate your efforts on behalf of myself and the University. I hope you can respect my position and opinion. I am in the process of putting together a truly "independent" and "expert" source of re-evaluation in consultation

with my co-investigators. When I have done so, I will let you know so that, in accordance with the IRB's conclusions and recommendations, the CRU and the School of Medicine can provide support for this evaluation.

Sincerely,

Jan

From: "Scott Compton, Ph.D." <compt004@duke.edu>
Date: Monday, October 26, 2020 at 12:55 PM
To: "Wei Jiang, M.D." <wei.jiang@duke.edu>
Subject: A Zoom to discuss next steps Re: REMIT

Hi Jan,

I hope this email finds you well. I was hoping we could find a time to Zoom about the next steps re: the REMIT study. One of the last things, based on the Standing Faculty Committee, is to send a letter to JAMA letting them know about the re-analysis and seeking their guidance about next steps. I'd like to talk through this process with you.

Are you around this week? If so, can you send me some times that might work for you?

Much thanks,
Scott

Scott Compton, Ph.D.
Associate Professor
Director, Clinical Research Unit (CRU)
Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine
Associate Professor of Psychology & Neuroscience, Duke University
Telephone: (919) 668-0063

From: Scott Compton, Ph.D. <compt004@duke.edu>
Sent: Tuesday, November 3, 2020 11:11 AM
To: Wei Jiang, M.D. <wei.jiang@duke.edu>
Subject: Re: A Zoom to discuss next steps Re: REMIT

Hi Jan,

Just a follow-up regarding the email below. It is important that we meet. Can you send me some times that might work for you this week? Hope you are doing well.

Much thanks!
Scott

Scott Compton, Ph.D.

From: Jean Beckham, Ph.D. <beckham@duke.edu>
Sent: Wednesday, November 4, 2020 10:55 AM
To: Wei Jiang, M.D. <wei.jiang@duke.edu>
Cc: Scott Compton, Ph.D. <compt004@duke.edu>; Dr Moira Rynn, M.D. <moira.rynn@duke.edu>
Subject: Can you please set up a time to discuss the next steps in contacting the journal with Scott?
Importance: High

Hi Jan,
I'm hoping you can get together with Scott and discuss the next step with the primary outcomes paper. We'd like to get this settled.
Thank you so much!
Jeannie

Sent from my iPhone

On Nov 4, 2020, at 12:36 PM, Wei Jiang, M.D. <wei.jiang@duke.edu> wrote:

Got it. Thank you, Jeannie. Jan

From: Jean Beckham, Ph.D. <beckham@duke.edu>
Sent: Wednesday, November 4, 2020 12:41 PM
To: Wei Jiang, M.D. <wei.jiang@duke.edu>
Cc: Scott Compton, Ph.D. <compt004@duke.edu>; Dr Moira Rynn, M.D. <moira.rynn@duke.edu>
Subject: Re: Can you please set up a time to discuss the next steps in contacting the journal with Scott?

Thank you Jan! I really appreciate it.
Jeannie

WJ's reply to Scott Compton at 12:33, 11/04/20

Hey Scott,

I have been in ED service last week and are under a couple of deadline now. I will get back to you ASAP.

Best, Jan

From: Scott Compton, Ph.D. <compt004@duke.edu>
Sent: Wednesday, November 4, 2020 1:29 PM
To: Wei Jiang, M.D. <wei.jiang@duke.edu>
Subject: Re: A Zoom to discuss next steps Re: REMIT

Thanks Jan. I already sent some times for tomorrow and Friday. If none of those work, just let me know and we can look at next week.

Best, Scott

Scott Compton, Ph.D.
Associate Professor
Director, Clinical Research Unit (CRU)
Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine
Associate Professor of Psychology & Neuroscience, Duke University
Telephone: (919) 668-0063

From: "Wei Jiang, M.D." <wei.jiang@duke.edu>
Date: Wednesday, November 4, 2020 at 4:31 PM
To: "Scott Compton, Ph.D." <compt004@duke.edu>
Subject: RE: A Zoom to discuss next steps Re: REMIT

Hey Scott, I need to catch up with a couple of tasks at present. Let me get back to you before the end of this weekend or early next Monday for this quest of you. Best, Jan

---

From: Scott Compton, Ph.D. <compt004@duke.edu>
Sent: Wednesday, November 4, 2020 4:35 PM
To: Wei Jiang, M.D. <wei.jiang@duke.edu>
Cc: Dr Moira Rynn, M.D. <moira.rynn@duke.edu>
Subject: Re: A Zoom to discuss next steps Re: REMIT

Thanks Jan. Just for your planning purposes, our call should take no more than 10-15 minutes. I wanted to review with you verbally the remaining steps that need to be taken.

Much thanks,
Scott

Scott Compton, Ph.D.
Associate Professor
Director, Clinical Research Unit (CRU)
Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine
Associate Professor of Psychology & Neuroscience, Duke University
Telephone: (919) 668-0063

From: Wei Jiang, M.D.
Sent: Wednesday, November 4, 2020 4:37 PM
To: Scott Compton, Ph.D. <compt004@duke.edu>
Cc: Dr Moira Rynn, M.D. <moira.rynn@duke.edu>
Subject: RE: A Zoom to discuss next steps Re: REMIT

I see. Will you please summarize what you need to inform me in a message for me? Thank you. Jan

---

From: Scott Compton, Ph.D. <compt004@duke.edu>
Sent: Wednesday, November 4, 2020 5:55 PM
To: Wei Jiang, M.D. <wei.jiang@duke.edu>
Cc: Dr Moira Rynn, M.D. <moira.rynn@duke.edu>
Subject: Re: A Zoom to discuss next steps Re: REMIT

Hi Jan,

Sure, happy to do this via email. I wanted to review the letter that we wrote on your behalf that needs to be sent to the editor of JAMA, as well as the letter for you to send to your co-authors on the primary outcome paper alerting them of this situation and that JAMA may be contacting them.

We need to move forward with the corrective actions made by the Standing Faculty Committee regarding the REMIT project. Specifically, we need to let the editor of JAMA know about the findings from the internal review and the results from the re-analysis conducted by DCRI on the smaller sample.

Attached are the two letters. Please sign and submit these via email by 12:00pm on Monday, Nov 9, 2020. When you send the emails, please cc Moira Rynn, Geeta Swamy, Donna Kessler, and me. If you do not submit the letters by the deadline, I will do so on your behalf Monday afternoon.

Please let me know if you have any additional questions or need clarification. I will gladly help you. I understand that this will likely be difficult, yet we need to be in compliance with the recommendations of the Standing Faculty Committee.

Best,
Scott

Scott Compton, Ph.D.
Associate Professor
Director, Clinical Research Unit (CRU)

Attachments:
1-Letter drafted by Scott Compton, Ph.D., to JAMA editors for signature by Wei Jiang, M.D.
2-Letter drafted by Scott Compton, Ph.D., to co-authors of REMIT study for signature by Wei Jiang, M.D.

Duke Psychiatry & Behavioral Sciences
Duke University School of Medicine

LETTER 1: **CONFIDENTIAL**

October 26, 2020

To: Dr. Howard Bauchner

Re: *JAMA*. 2013;309(20):2139-2149. doi:10.1001/jama.2013.5566

Dear Dr. Bauchner,

I am contacting you regarding the May 22, 2013 *JAMA* publication entitled, "Effect of escitalopram on mental stress-induced myocardial ischemia: Results of the REMIT trial." The REMIT trial examined the effects of 6 weeks of escitalopram treatment vs. placebo on mental-stress-induced myocardial ischemia (MSIMI).

After the publication, a recent institutional internal review determined that 26 of 127 (20.5%) study participants enrolled did not meet all inclusion/exclusion criteria specified in the protocol. For example, one key inclusion criteria required that participants withhold their beta-blocker medication prior to the stress test and be physically capable to perform the exercise stress tests. However, many of these participants did not hold their beta-blocker medication before the stress tests or were physically unable to perform the exercise stress tests.

A re-analysis of the study results using data from only those participants who met all inclusion/exclusion criteria showed that some of the results reported in the publication were no longer statistically significant. In particular, the difference in the incidence of MSIMI among participants receiving escitalopram compared to those receiving placebo did not reach statistical significance, and the overall magnitude of the effect was smaller (details are provided in **Appendix A** where results from the re-analysis are presented next to those published in JAMA manuscript). Additionally, some errors were identified in the published tables (listed below).

a. The number of participants listed in Table 1 as "total with history of diabetes" was actually "total **without** history of diabetes."
b. The "resting heart rate" in Table 2 was actually "weight in kg."
c. The standard deviations for "trait anxiety" in Table 2 were incorrect.
d. The "resting negative and positive affect" in Table 2 were actually "mean negative and positive affects."
e. The p-values in Table 3 were labeled as Fischer's exact tests but were actually chi-square tests.
f. The data presented in Table 4 has an extra placebo patient.
g. The models in Table 5 were not adjusted for age even though the footnote indicates that they were.

Based on the information above, we believe the publication may need to be corrected or retracted. We are seeking your guidance and recommendations on next steps.
If you have questions or need additional information, please feel free to contact me at your earliest convenience. I can be reached by phone at (919) 123-4567 and by email at wei.jiang@duke.edu.

Sincerely,

Wei Jiang, M.D.
Professor of Psychiatry and Behavioral Sciences
Duke University Medical Center

CC: Scott Compton PhD, Director, Clinical Research Unit, Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine
Moira Rynn MD, Chair, Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine
Geeta Swamy MD, Associate Vice President for Research, Duke University; Vice Dean for Scientific Integrity, Duke University School of Medicine
Donna Kessler PhD, Research Integrity Officer, Duke University

APPENDIX A

Table 4. MSIMI Defined by Wall Motion Abnormality and/or LVEF at Baseline and Endpoint

	From Original Publication (N=127)				From Reanalysis After Removing Patients Failing to Meet Inclusion or Exclusion Criteria (N=101)			
Variable	**Escitalopram**	**Placebo**	**OR (95% CI)**	**P-value**	**Escitalopram**	**Placebo**	**OR (95% CI)**	**P-value**
Baseline, n (%)								
Overall MSIMI	63/64 (98.4%)	63/63 (100%)		>.99	51/52 (98.1%)	49/49 (100%)		>.99[1]
Wall motion abnormality only	37/64 (57.8%)	42/63 (66.7%)			27/52 (51.9%)	35/49 (71.4%)		
LVEF reduction ≥ -8% only	9/64 (14.1%)	9/63 (14.3%)			8/52 (15.4%)	8/49 (16.3%)		
Both	17/64 (26.6%)	12/63 (19.1%)			16/52 (30.8%)	6/49 (12.2%)		
Endpoint, n (%)								
Overall MSIMI	37/56 (66.1%)	47/56 (83.9%)	2.68 [1.09, 6.61]	.03	29/46 (63.0%)	34/44 (77.3%)	1.99 [0.79, 5.02]	.14
Adjusted per-protocol, n (%)			2.57 [0.99, 6.66]	.05			2.16 [0.80, 5.83]	.13
Wall motion abnormality (WMA) only	22/56 (39.3%) [30.2, 48.3]	32/56 (57.1%) [47.9, 66.3]			16/46 (34.8%) [21.0, 48.6]	23/44 (52.3%) [37.51, 67.0]		
LVEF reduction ≥ -8% only	3/56 (5.4%) [1.2, 9.5]	4/56 (7.1%) [2.3, 11.9]			2/46 (4.3%) [0.5, 14.8]	2/44 (4.6%) [0.56, 15.5]		
Both	12/56 (21.4%) [13/8, 29.0]	11/56 (19.6%) [12.3, 27.0]			11/46 (23.9%) [11.6, 36.2]	9/44 (20.4%) [8.54, 32.4]		
Imputed primary end point, %								
No MSIMI	34.2% [31.6, 36.8]	17.5% [15.4, 19.6]	2.62 [1.06, 6.44]	.04	38.9% [24.3, 53.4]	24.5% [10.3, 38.7]	1.97 [0.77, 5.02]	.16

1. P-value from Fisher's exact test.

Note: With the reduced population, the lower rate of MSIMI at endpoint in escitalopram participants does not reach statistical significance and the magnitude of the effect is attenuated. The odds ratio for the association between escitalopram treatment and no MSIMI was published to be 2.68 in completers (2.62 when imputed) and we observe an odds ratio of 1.99 in the reduced sample (1.97 when imputed). If a reason is not found and the endpoint is changed for the one placebo patient who the manuscript classified as having endpoint MSIMI but whom we do not see the evidence for that classification, then the odds ratio in the original manuscript would have been 2.36 in completers. P-values that were less than 0.05 in the publication are greater than 0.1 in the subset deemed eligible.

Duke Psychiatry & Behavioral Sciences
Duke University School of Medicine

LETTER 2

CONFIDENTIAL

October 26, 2020

To: Eric Velazquez, Maragatha Kuchibhatla, Zainab Samad, Stephen Boyle, Cynthia Kuhn, Richard Becker, Thomas Ortel, Redford Williams, Joseph Rogers, Christopher O'Connor

Re: *JAMA*. 2013;309(20):2139-2149. doi:10.1001/jama.2013.5566

Dear Co-Authors,

I am contacting you regarding the May 22, 2013 *JAMA* publication entitled, "Effect of escitalopram on mental stress-induced myocardial ischemia: Results of the REMIT trial." A recent institutional internal review determined that 26 of 127 (20.5%) study participants enrolled did not meet all inclusion/exclusion criteria specified in the protocol. As you know, one key inclusion criteria required that participants withhold their beta-blocker medication prior to the stress test and be physically capable to perform the exercise stress tests. However, many of these participants did not hold their beta-blocker medication before the stress tests or were physically unable to perform the exercise stress tests.

Because of this finding, a re-analysis of the study results using data from only those participants who met all inclusion/exclusion criteria was undertaken. The results from this re-analysis showed that some of the findings reported in the published manuscript were no longer statistically significant. In particular, the difference in the incidence of MSIMI among participants receiving escitalopram compared to those receiving placebo did not reach statistical significance, and the overall magnitude of the effect was smaller (details provided in **Appendix A** Table 4). Additionally, some other errors were identified in the published tables. Based on the information above, I am reaching out to the editor at JAMA, Dr. Howard Bauchner, to seek his guidance about possible next steps.

I wanted each of you to be aware of the situation, particularly as JAMA may contact you at some point. I will also keep you informed about any new developments, including the response I receive from JAMA.

Sincerely,

Wei Jiang, M.D.
Professor of Psychiatry and Behavioral Sciences
Duke University Medical Center

CC: Scott Compton PhD, Director, Clinical Research Unit, Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine
Moira Rynn MD, Chair, Department of Psychiatry and Behavioral Sciences, Duke University School of Medicine

APPENDIX A

Table 4. MSIMI Defined by Wall Motion Abnormality and/or LVEF at Baseline and Endpoint

	From Original Publication (N=127)				From Reanalysis After Removing Patients Failing to Inclusion or Exclusion Criteria (N=101)		
Variable	**Escitalopram**	**Placebo**	**OR (95% CI)**	**P-value**	**Escitalopram**	**Placebo**	**OR (95% CI)**
Baseline, n (%)							
Overall MSIMI	63/64 (98.4%)	63/63 (100%)		>.99	51/52 (98.1%)	49/49 (100%)	
Wall motion abnormality only	37/64 (57.8%)	42/63 (66.7%)			27/52 (51.9%)	35/49 (71.4%)	
LVEF reduction ≥ -8% only	9/64 (14.1%)	9/63 (14.3%)			8/52 (15.4%)	8/49 (16.3%)	
Both	17/64 (26.6%)	12/63 (19.1%)			16/52 (30.8%)	6/49 (12.2%)	
Endpoint, n (%)							
Overall MSIMI	37/56 (66.1%)	47/56 (83.9%)	2.68 [1.09, 6.61]	.03	29/46 (63.0%)	34/44 (77.3%)	1.99 [0.79, 5.02]
Adjusted per-protocol, n (%)			2.57 [0.99, 6.66]	.05			2.16 [0.80, 5.83]
Wall motion abnormality (WMA) only	22/56 (39.3%) [30.2, 48.3]	32/56 (57.1%) [47.9, 66.3]			16/46 (34.8%) [21.0, 48.6]	23/44 (52.3%) [37.51, 67.0]	
LVEF reduction ≥ -8% only	3/56 (5.4%) [1.2, 9.5]	4/56 (7.1%) [2.3, 11.9]			2/46 (4.3%) [0.5, 14.8]	2/44 (4.6%) [0.56, 15.5]	
Both	12/56 (21.4%) [13/8, 29.0]	11/56 (19.6%) [12.3, 27.0]			11/46 (23.9%) [11.6, 36.2]	9/44 (20.4%) [8.54, 32.4]	
Imputed primary end point, %							
No MSIMI	34.2% [31.6, 36.8]	17.5% [15.4, 19.6]	2.62 [1.06, 6.44]	.04	38.9% [24.3, 53.4]	24.5% [10.3, 38.7]	1.97 [0.77, 5.02]

1. P-value from Fisher's exact test.

Note: With the reduced population, the lower rate of MSIMI at endpoint in escitalopram participants does not reach statistical significance and the magnitude of the effect is The odds ratio for the association between escitalopram treatment and no MSIMI was published to be 2.68 in completers (2.62 when imputed) and we observe an odds rat the reduced sample (1.97 when imputed). If a reason is not found and the endpoint is changed for the one placebo patient who the manuscript classified as having endpoin whom we do not see the evidence for that classification, then the odds ratio in the original manuscript would have been 2.36 in completers. P-values that were less than publication are greater than 0.1 in the subset deemed eligible.